Harvard Medicine
SPRING 2010

Accounting for Taste

Harvard doctors explore the 5 senses

SPRING 2010 VOLUME 83 NUMBER 1

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COVER PHOTOGRAPH: LEOMBRUNO-BODI/CONDÉ NAST ARCHIVE/CORBIS

Special Report

THE FIVE SENSES

From the Dean

THOUGHTS ON INNOVATION

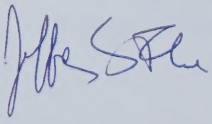
The last time this magazine was redesigned, more than a decade ago, the editor felt justified trepidation. The late Francis Moore '39, the intimidating mentor to generations of Harvard surgical residents and staunch *Harvard Medical Alumni Bulletin* devotee, had admonished her not to change *anything*. The *Bulletin* was sacrosanct, he said, with sonorous emphasis, "like Shakespeare and the Bible."

The editor survived the redesign—Moore ended up applauding the changes, with a caution not to let the designer go wild—and remains with the magazine. The magazine itself, though, now bears a fresh look, a new title, and an expanded editorial focus. In making changes, we've been mindful that some readers have been receiving the publication for seven decades. That's tradition, and tampering with tradition can be tricky. But at Harvard Medical School, we pride ourselves on building on foundations to enhance the future, not stand in its way.

And so, in this spirit, we give you *Harvard Medicine*. With one leg up on Aristotelian tradition, this first issue in the new format looks not just at the five senses, but beyond them. In these pages you'll find a surgeon's exploration of the sixth sense, an accounting of additional senses, and meditations on mingled senses: the hearing of sight, the feeling of sound, the synesthetic links between luminosity and speech.

Through its explorations of medicine and science at HMS, *Harvard Medicine* aims to capture both their meaning and their unfolding drama. Rest assured: The devotion to doctors' voices and the literary aspirations you have come to expect in the magazine will remain. But, after surveying readers, we're expanding our content. With this new iteration we plan to explore more deeply than before the work of the HMS community and its power to make contributions to human health.

Ultimately, the continuing success of this magazine will depend on your feedback. Please join our Readers' Panel—visit harvardmedicine.hms.harvard.edu/feedback.php—and regularly share your comments and ideas. You may also want to sample online-exclusive content on the magazine's website. Above all, we invite you to savor the insights and innovations that Harvard's doctors and scientists offer in these pages.



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Harvard Medicine, formerly known as the *Harvard Medical Alumni Bulletin*, is published three times a year at 25 Shattuck Street, Boston, MA 02115
Publishers: Harvard Medical School and Harvard Medical Alumni Association

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Web: harvardmedicine.hms.harvard.edu
Third class postage paid at Boston, Massachusetts. Postmaster, send form 3579 to 25 Shattuck Street, Boston, MA 02115
ISSN 2152-9957 · Printed in the U.S.A.

PHOTO: GRAHAM GORDON RAMSAY

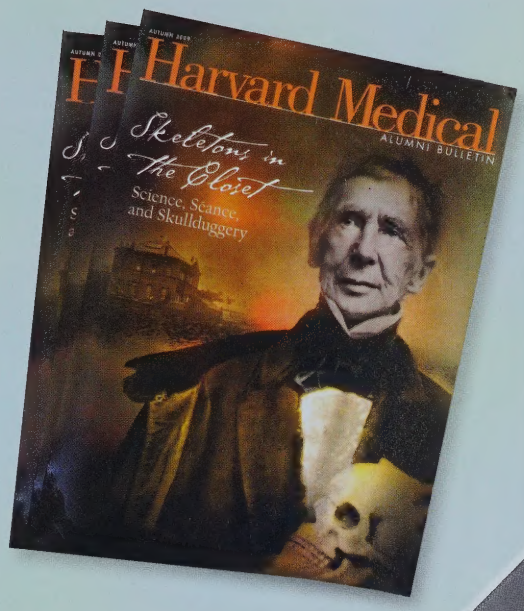
Letters to the Editor

SECOND OPINIONS FROM OUR READERS

Strong Medicine

Congratulations on the "Skeletons in the Closet" issue—one of your best ever!

CHARLES HARTNESS '82
ATHENS, GEORGIA



Magical Mystery Cure

Your article on medical mysteries in the Autumn 2009 issue brought to mind a curious case I encountered early in my career. In the 1960s, a family brought their five-year-old daughter to my new practice in Maine. Her staggering gait and slurred speech alarmed me. Thinking it might be a brainstem tumor, I referred her to Children's Hospital in Boston, where I had recently completed my training.

There, the neurologist and residents checked her over as best they could in the days before MRIs. She gradually improved and they eventually discharged her, assuming that she had suffered some sort of transient cerebellitis.

Several weeks later she was back in my office with the same symptoms. After reviewing the thorough family and social history I had taken (in proper Harvard fashion), it occurred to me that an aunt who lived with the family might be taking Dilantin for her epilepsy; an overdose of the drug could certainly cause the girl's symptoms. My simple suggestion to the family produced another recovery and prevented other recurrences.

CHARLES E. BURDEN '59
AUGUSTA, MAINE

A Whiter Shade of Pale

The introduction in the "Skeletons in the Closet" issue caught my eye, especially the mention of how John Collins Warren's bones had been "carefully preserved" and "whitened" according to his own instructions.

While studying for an anatomy exam at Dartmouth Medical School in 1951, before I transferred to HMS, I spent an afternoon in a darkened museum surrounded by specimen cabinets. In one cabinet I found a strikingly white, porcelain-light skull with hinged trapdoors that opened to labeled cranial nerves and foramina. Arteries and veins had been removed, and their paths along the skull's inner surface had been diagramed in red and blue. I later revisited the skull and found a trapdoor I had overlooked. Beneath it was inscribed "Prepared by Oliver Wendell Holmes—1840." Holmes, HMS Class of 1836, had been an anatomy professor at Dartmouth for two years before returning to Harvard in 1840.

I have been teaching anatomy at the Florida State University College of Medicine since retiring from general surgery in 1997. I have seen many skull preparations but none as exquisite as that one. Holmes's whitening process was special; demineralization likely explained the lightness. Unfortunately, the skull can no longer be found. There is a good chance, though, that a similar trapdoor skull that Holmes produced is in a specimen cabinet at Harvard. Such a skull would be a welcome addition to the School's Warren Anatomical Museum.

Meanwhile, I suspect that Holmes helped orchestrate the whitening of Warren's bones.

JAMES CAVANAGH '54
TALLAHASSEE, FLORIDA

A Pressured Gage

The Autumn 2009 *Bulletin* brought back memories from 50 years ago, when I was based at the Warren Anatomical Museum, where Phineas Gage's skull and tamping iron were on display. The trajectory of the wound suggested injury to the left frontal lobe and perhaps to the medial aspect of the right frontal lobe. After his accident, Gage was reported to have experienced changes to his personality but not to his language function.

The newly discovered photograph of Gage shows him holding his tamping rod as would a left-handed baseball batter—at the left shoulder, left hand on top—and with his hair parted on the right in the style of a left-handed man of that era. He may have adopted his hairstyle after his injury, of course, to conceal his cranial defect.

If, as the photograph suggests, Gage was right-cerebral dominant, that would better help explain his personality change and his intact language function.

SIMEON LOCKE, MD
BOXFORD, MASSACHUSETTS

LIGHTNESS OF BEING: In the aftermath of the Haiti earthquake, HMS physicians teamed with local and international health care workers to help Haitians with the long recovery ahead.

PHOTO: ROBERT SHERIDAN

HARVARD IN HAITI

More than 500 affiliated doctors and nurses have pitched in to help

On January 12, the ground beneath Louise Ivers began to shift. The HMS assistant professor of medicine and clinical director in Haiti for Partners In Health was in Port-au-Prince discussing disaster preparedness when a 7.0-magnitude earthquake struck. Dazed, Ivers watched as nearby buildings collapsed around her. As she picked herself up off the floor, a bystander's simple plea snapped her from her trance: "I wish someone was a doctor!" Ivers, like hundreds of other members of the Harvard medical community, has been responding to that call ever since.

Stories such as this illustrate the "living links between Harvard and Haiti," says Paul Farmer '90, chair of the Department of Global Health and Social Medicine and cofounder of Partners In Health (PIH). Ties between PIH and the impoverished country run long and deep. The nonprofit organization has been working in Haiti for more than 20 years to help prevent and treat such diseases as AIDS and multi-drug-resistant tuberculosis. When the quake hit, PIH—with its network of health services and workers—became a chief international resource for coordinating the emergency response. Although the group's own facilities were largely untouched by the quake, other medical institutions weren't so lucky: A nursing school—one of three in the country—was destroyed, killing some 150 students, nearly the entire second-year class.

Losses like this reinforce the need for international aid, says HMS Dean Jeffrey Flier. Much of that help has come from the Harvard community, with roughly 500 doctors and nurses offering assistance. The Harvard Humanitarian Initiative has coordinated a group of medical, surgical, and public health volunteers within Partners HealthCare System who have deployed to Haiti. Massachusetts General Hospital and Brigham and Women's Hospital have sent similar teams. Back at home, the University has established the Harvard Haiti Emergency Relief Fund for Employees, which collects donations from the Harvard community to provide financial assistance to the nearly 100 employees with family members in Haiti.

Meanwhile, PIH has expanded its focus to include long-term recovery and rebuilding initiatives and improving the country's public health system through the Stand with Haiti Fund.

"Haiti needs to be built back better and stronger than before," says Farmer. "A university like ours can offer its own brand of pragmatic solidarity and set the highest standards for research, teaching, and service."

TO LEARN MORE

The Harvard community continues to offer aid to the people of Haiti. For more information, visit the following:

- Harvard Medical School's Response to the Haiti Earthquake (includes details about the School's work and video clips of updates by Paul Farmer and his colleagues): hms.harvard.edu/public/haiti
- Partners In Health's Stand with Haiti Fund: www.standwithhaiti.org
- The Harvard Humanitarian Initiative: www.hhi.harvard.edu

THE GREAT DEBATE: A forum on health care reform brought together the disparate viewpoints of such experts as, from left, David Goldhill, Allan Detsky, and David Cutler.

PHOTO: JUSTIN KNIGHT

"Insurance is the most administrative, costly, financially distortive form of financing that exists. This is why, outside of health care, insurance is only used for things that are rare, unpredicatable, and major."

HEALTHY DEBATE

A panel of experts wrangle with the health care reform dilemma

For those who enjoy political theater, the national health care debate has not disappointed. But good theater and cogent debate rarely coexist. To add a measure of thoughtful discussion to the mix, HMS Dean Jeffrey Flier invited a group of experts to debate the subject at the School in January.

The presenters, with one exception, were not hopeful about the prospects of meaningful reform, citing impediments ranging from a flawed funding structure to a dysfunctional political process.

According to Allan Detsky '78, professor of health care policy at the University of Toronto, governmental structure is the main problem facing U.S. health care reform. He contended that it is far easier to approve legislation under a parliamentary system in which the executive and legislative branches are aligned within a majority government.

David Goldhill, author of an article in *The Atlantic* that indicts the nation's health care system, began exploring the health care industry after his elderly father died from a hospital-acquired infection. He views the recent bill as expanding a broken system focused on coverage, not care.

"Insurance is a form of finance," he explained. "It is the most administrative, costly, financially distortive form of financing that exists. This is why, outside of health care, insurance is only used for things that are rare, unpredictable, and major. In health care we use insurance for everything."

Goldhill's recommendations for reform include establishing a national policy that would require people to save for their health care and pay for part of it, and drawing consumers into the system.

David Cutler, a Harvard professor of economics who was senior health care adviser to Barack Obama's presidential campaign, expressed cautious optimism. The answer to inefficiency and waste in the health care system, he said, is to target the supply side (providers), which would be more precise and effective than targeting the demand side (patients). Data show that hospital admissions drop when hospitals receive incentives not to keep patients for long periods. But if you target the demand side with price incentives, Cutler explained, patients often will not act in their best interests and instead switch to cheaper and less effective medications and therapies.

The recent plan, which includes some supply-side incentives, represents "a path, not a leap," Cutler cautioned. "Passing the legislation is only 15 percent of the challenge. The remaining 85 percent is making it work."

Daniel Kessler, the final speaker, disagreed with Cutler. A professor of management at Stanford University, Kessler claimed that the proposals would cause fiscal problems and that having health insurance does not necessarily improve health. The plan, he contended, would create another middle-class entitlement program; massive work disincentives by generating an implicit marginal tax rate; and openings for increased government involvement in people's private lives.

Kessler conceded, however, that he had no workable alternative to offer.

—David Cameron

The latest HMS *Dean's Report*, which features work ranging from global health outreach to biologically inspired engineering, is available online. >> hms.harvard.edu/deans_report

BACK TO SCHOOL

Chin will lead the effort to find new ways to translate research

This May, one of Harvard Medical School's distinguished graduates is returning to the fold. After a decade-long stint at Eli Lilly and Company, where most recently he served as senior vice president for discovery research and clinical investigation, William Chin '72 will rejoin HMS as executive dean for research. In this newly created position, the molecular endocrinologist will have overarching responsibility for the School's biomedical investigation.

In his new role, Chin will spearhead efforts to design and implement a vision for research at HMS, focusing on interdisciplinary investigations that cross departmental and institutional boundaries and advance translational research and therapeutics. He will also hold an academic appointment as an HMS professor of medicine.

Chin has had a long and deep relationship with his alma mater and its affiliates. After training at Beth Israel Hospital and Massachusetts General Hospital, he served on the faculty in the Department of Medicine at Brigham and Women's Hospital. He later became chief of the genetics division at that hospital, as well as a Howard Hughes Medical Institute investigator and a professor of medicine and of obstetrics, gynecology, and reproductive biology at HMS. Chin has published nearly 300 papers, chapters, and books and has received numerous awards for his research and mentorship.

Many of Chin's investigations have exemplified the concept of translational research, applying basic scientific discoveries to animals and, ultimately, humans. This approach, says HMS Dean Jeffrey Flier, makes Chin a fitting choice to develop and guide new research initiatives. "One of Bill's highest priorities," Flier says, "will be to help find new ways to transform the world's most vital biomedical research into therapies that can directly improve human health."

At a time when industry ties to academe are under scrutiny, Flier adds, Chin's experience at Lilly will serve HMS well. Chin will develop a coherent strategy for the School's scientific interaction with industry, ensuring that it adheres to the HMS Faculty Policy on Conflicts of Interest and Commitment. "There are very few people capable of rising to meet such challenges," says Flier. "I'm thrilled that Bill will be joining the HMS leadership team."

WILLIAM CHIN

Thoughts that Count

Got a bright idea? Harvard Catalyst, the Harvard Clinical and Translational Science Center, wants to know. Using federal stimulus funding from the National Institutes of Health, the group has joined with InnoCentive, a global platform for innovation contests, to launch a series of challenges aimed at uncovering novel solutions to thorny scientific problems. Such contests, which have successfully fostered innovation in the business sector, may spark investigations in medicine as well.

The first contest, earlier this year, challenged the entire Harvard community—including faculty, students, and staff—to brainstorm fresh ideas related to type 1 diabetes. This condition "has touched many people at Harvard and elsewhere," says Eva Guinan '80, an HMS associate professor of pediatrics at the Dana–Farber Cancer Institute and one of the project's leaders. "As a result, they may have questions or ideas that could help spawn new collaborations and areas for research."

To sweeten the deal, Harvard Catalyst offers between $2,500 and $10,000 in prize money for ideas that the review panel deems most promising. For more information on this and future contests, visit innocentive.com/harvardcatalyst.

PHOTO: LILLY ARCHIVES; ILLUSTRATION: MICHAEL KLEIN

BENCHMARKS

DISCOVERY AND INNOVATION AT HMS

ILLUSTRATION: SARAH HOLLANDER/THEISPOT.COM; PHOTO: NACIVET/TAXI/GETTY IMAGES

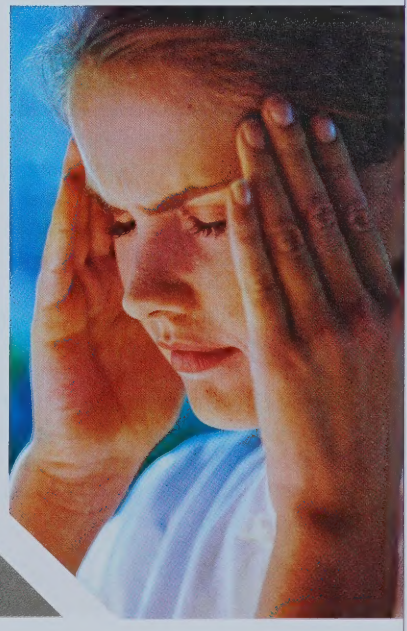
BRAIN STORM WARNINGS

A new forecast for early stroke recurrence goes by the numbers

A Web-based tool developed at Massachusetts General Hospital may provide a much-needed 90-day forecast of the risk for a second stroke among people who have suffered one such calamity. A stroke soon after an initial one increases the chance of death or severe disability, writes Hakan Ay, an HMS assistant professor of radiology, in his January 12 article in *Neurology*. The tool—the recurrence risk estimator at 90 days—scores risk by assessing data such as age, history of transient ischemic attacks, cause of first stroke, and brain-scan information. The higher the score, the greater the chance of a repeat attack. The study showed that long-term stroke predictors—smoking, diabetes, and hypertension—are not predictive of short-term recurrences.

Tricks of the Light

For spiritualists, auras are said to provide luminous insight, but for those who suffer migraines, auras can have sinister connotations. Nearly 20 percent of the population suffers these devastating headaches, with one-third experiencing premigraine visual disturbances. Past studies have linked migraines with aura to an increased risk for a vascular ischemic event. But a study of more than 27,000 women in the January issue of *Headache* found more nuanced associations. Led by Markus Schürks, an HMS instructor of medicine at Brigham and Women's Hospital, researchers found a doubled risk for cardiovascular disease, myocardial infarction, and ischemic stroke among women who experience migraines with auras compared with those with aura-free migraines. The findings, says Schürks, suggest that women with aura-plagued migraines should avoid smoking and contraceptives with estrogen.



Anorexics have been found to have excess fat in their bone marrow.
>> harvardmedicine.hms.harvard.edu/benchmarks.php

THE INSULTS OF INJURY

Trauma-related mitochondrial damage may trigger inflammation

Mitochondria are minute organelles that float, sometimes by the thousands, within the cytoplasm of our cells. Distant relatives of bacteria, these tiny powerhouses produce the energy-rich molecules that our cells consume for such demanding activities as replication, movement, and repair. But despite their intracellular residency, mitochondria remain genetically discrete, housing DNA that is molecularly unrelated to that within the cell's own nucleus.

Research at Beth Israel Deaconess Medical Center now indicates that it may be precisely this part-and-apart nature of mitochondria that makes them culpable in a form of inflammation that arises from cellular injury and unregulated cell death rather than from infection.

"Blunt-force trauma," says team member Carl Hauser, an HMS visiting professor of surgery and a trauma and critical-care specialist at the medical center, "can kill significant amounts of tissue, as can burns, chemotherapy, and many diseases. We wondered whether tissues that die from trauma release a sort of molecular debris not usually encountered by the body's immune system."

In research published in the March 4 issue of *Nature*, Hauser and colleagues report that detritus, particularly mitochondria, from traumatized cells triggered a systemic inflammatory response that—when tested in human white blood cells, rats, and mice—was akin to infection-related sepsis in humans. Clinically, traumatic injury to tissue initiates an immune response much like that waged against foreign invaders such as viruses or bacteria. Unlike immune responses acquired through vaccinations and other preventive measures, the body's response to foreign material is innate, cued from birth to respond immediately to the molecular patterns of external pathogens—like the patterns carried by that bacterial relative, the mitochondrion. In trauma-induced immune responses, however, the body's fight focuses on itself. Thus, when freed from their cellular confines, the mitochondrial residents that power a cell's health and functioning become tools to its destruction.

The findings could spur the development of new tests to discriminate infective from non-infective inflammation as well as new strategies for trauma management.

Bringing Home Baby

Placing infants with foster families rather than in institutions provides them with long-term cognitive benefits. When a research team from Harvard Medical School, the University of Wisconsin, and the University of Minnesota compared cognitive development in eight- and nine-year-olds who had been placed in foster care as infants with those raised in their birth families, it found no difference in visual memory and attention and impulse control. Yet same-aged children who had lived in institutions their first year tested lower than either group, despite subsequent years of family life. The study appeared in the January/February issue of *Child Development*.

PHOTO: AMANDA ROHDE/ISTOCKPHOTO.COM

Here Be Dragons

Cancers spring in large part from changes in the numbers of copies of specific regions of the genome, according to research by an HMS team from the Dana–Farber Cancer Institute and the Broad Institute of Harvard and MIT. The team discovered this shared heritage by assembling a genome-scale map of more than 3,000 specimens of 26 cancer types. The map showed that, compared with genetic material from normal tissue, the DNA from the profiled tumor types had more than a hundred sites of missing or duplicated genetic information in common. The universality of the shared errors surprised the researchers.

"The degree to which so many alterations are shared," says team leader Matthew Meyerson '89, "suggests that, in the future, a driving force behind cancer treatment will be common genomic alterations, rather than tumors' tissue of origin."

Meyerson, an HMS professor of pathology at Dana–Farber and a senior associate member of the Broad Institute, adds that the continuing technological advances will make it possible to "decode the genomes of thousands of cancers and reveal every genomic change."

The study, published in the February 18 issue of *Nature*, sheds light on the molecular bases of cancers, information useful to research on more effective therapies.

"Our findings suggest that, in the future, a driving force behind cancer treatment will be common genomic alterations, rather than tumors' tissue of origin."

RELIEF CAPSULE: Michelle Holmes has found that over-the-counter analgesics offer hope to women with breast cancer.

PHOTOS: STEPHANIE MITCHELL/HARVARD NEWS OFFICE; LAST RESORT/PHOTODISC/GETTY IMAGES

ONE A DAY

Regular use of aspirin-like compounds has been found to halve the risk for breast cancer recurrence and death

The "take an aspirin" part of the doctor's maxim stays intact, but there may not be a need to call in the morning, at least not for women interested in the potential benefits found in research from Brigham and Women's Hospital. According to data gathered from more than 4,000 women who had been diagnosed with breast cancer, those who took aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) had a significantly reduced risk of experiencing a recurrence or dying from the disease. The study, published in the February 16 issue of the *Journal of Clinical Oncology*, also suggested that the protective effect was associated with the number of days per week that the women took the agents, with more days equaling lower risk.

The study used data collected from nurses who had enrolled in the hospital's landmark Nurses' Health Study and had been diagnosed with Stage I, II, or III breast cancer between 1976 and 2002. Researchers analyzed reports from these women about their frequency of aspirin use one year after their first diagnosis of breast cancer through June 2006 or their death, then adjusted for stage of cancer, menopausal status, body mass index, and cancer treatments. The result: a 50-percent-lower chance of death and of recurrence among those who took the drug. Women in the study reported taking the agents between one and seven days each week, with a lowered risk associated with two to five days of aspirin or six to seven days of other NSAIDs.

"More than 2 million women in the United States live with breast cancer, and their risk of death from this disease remains elevated even up to 15 years after diagnosis," says Michelle Holmes '81, an HMS associate professor of medicine at the Channing Laboratory at Brigham and Women's Hospital and lead author on the study. "More research is needed to determine how aspirin and other nonsteroidal anti-inflammatory drugs may work to prohibit the recurrence of this disease."

Delaying radiation after breast cancer surgery increases recurrence risk in older women. >> harvardmedicine.hms.harvard.edu/benchmarks.php

In Circulation

Technical improvements to a microchip-based device for detecting and analyzing tumor cells in the bloodstream are revealing cellular differences that may reflect a tumor's aggressiveness and long-term response to treatment. In the March 31 issue of *Science Translational Medicine*, researchers at Massachusetts General Hospital describe improvements to their CTC chip, which measures levels of circulating tumor cells, or CTCs, in the bloodstream. These advancements may allow better monitoring of how CTC levels react to treatment for prostate cancer and show key biologic properties of the cells.

Cone of Silence

Men under the age of 50 who take over-the-counter painkillers containing acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs) increase their risk of hearing loss, according to researchers at Brigham and Women's Hospital. Men in their forties who took two or more doses each week of acetaminophen doubled their risk for hearing loss. Similar aspirin doses raised risk more than 30 percent; for other NSAIDs, the risk increased 61 percent. The study appeared in March in the *American Journal of Medicine*.

PHOTOILLUSTRATION: C. J. BURTON/CORBIS

Amazing Grace

When a man lets his eyesight fail, his blindness reanimates a lost world.

~ *by* ELISSA ELY

My patient should not have gone blind. His glaucoma was treatable. When drops stopped working in one eye, a shunt was placed to relieve the pressure. When the shunt failed, the patient suspected sabotage; his ophthalmologist *wanted* him to go blind. It was a variant on the voodoo that had been cast on him for years and that had caused multiple hospitalizations since adolescence.

His ophthalmologist wished nothing but sight for him, of course. He was offered other ophthalmologists, other clinics. But he resisted. There would be no further shunts or any other eye treatment. His decision was absolute. He preferred to lose his vision; that much was under his control.

his monosyllables became lucid, animated monologues. We learned that he had read voraciously through his childhood and into the beginning of his psychiatric illness.

Large doses of the many antipsychotic medications he had taken for years could not persuade him otherwise.

His medical guardian was horrified. We all were. His decision was based on delusion; the consequences would be irreversible. Surely treatment could be forced. Many conversations were held, many consultations were sought. In the end, though, no surgeon would bind him to a table against his will and operate.

We watched as he gradually lost the sight that was savable. It was like the opposite of time-lapse photography—in slow motion, his view disappeared. He still visited our mental health clinic once a month for his psychiatry appointment, listing along the hall, bumping into doors. The staff in his group home tried to teach him to master a collapsible cane and enrolled him in a day program for the blind. Budget cuts promptly closed the program, but he would not have stayed, anyway; he knew the place was full of rapists.

In the clinic, he had presented himself as a quiet, stunted man with no interests: no friends, no hobbies, no habits. Given his circumstances, this attitude was sensible. Anyone hounded by hallucinations would find it hard to maintain a lively interest in the outer world. He was monosyllabic in meetings, and we assumed his private life was as vacant as his public one.

But we were wrong. When he could no longer see outside of himself, he began looking inward. Caution is necessary here—the vision metaphor is cheap—but he seemed to be looking back toward himself.

After he went blind, for the first time we heard him talk, not about voodoo and witchcraft, but about books. His monosyllables became lucid, animated monologues. We learned that he had read voraciously through his childhood and into the beginning of his psychiatric illness. Books had raised him. Holding his collapsed cane, he sat in the office and recalled his literary life. He wanted us to know it.

His reading had been precocious and furious, political and full of feeling, biographical and muscular. It was a nutritious life. But the words he had consumed had been clothed in flame: *Manchild in the Promised Land, The Autobiography of Malcolm X, Soul on Ice, The Fire Next Time, Native Son.* He had chosen the books deliberately, as if he had known he would have no time for dainty, pretty, peace-loving words. He had read the books raw; their passion and rage for life reflected his own.

When schizophrenia had taken hold, he had closed the book on his books and become preoccupied with inner violences. Then, when he lost his vision, he seemed to reopen the books. Of course we offered him an entire library on tape, lessons in Braille, any possible window into a future. He pleasantly assured us that he might consider our suggestions. Months have passed, and he is still pleasantly considering.

All his life, no one had known it, but he had been on fire.

Elissa Ely '88 is a psychiatrist at the Massachusetts Mental Health Center.

PHOTOILLUSTRATION: PAUL TAYLOR/STONE/GETTY IMAGES

BABY ON BOARD: The young participants in Charles Nelson's studies give us a glimpse into how facial recognition works.

PHOTO: MARGARET LAMPERT

SAVING FACE

Infants may be more skilled than adults at facial recognition

The six-month-old sits cradled on his mother's lap in the dark, watching images flash across the screen in front of him. But the colorful characters of *Sesame Street* and *Yo Gabba Gabba* aren't on view. Instead, the child, whom we'll call Tommy, is watching a series of human faces; an eye tracker is measuring his reactions as part of an ongoing study about facial recognition. It's the first of several visits Tommy will make to the Laboratory of Cognitive Neuroscience at Children's Hospital Boston. While the significance of his participation might be lost on the youngster—despite a mild cold, he sucks calmly on his pacifier throughout the hourlong session—his responses will aid scientists' understanding of how we develop the ability to recognize and process faces.

"Our faces contain a wealth of information, from our identity, age, gender, and race to our emotions and intentions," says Charles Nelson, the lab's director and an HMS professor of pediatrics and neuroscience. "For babies, who are preverbal, much depends on their ability to recognize and read faces."

In fact, infants may be more skilled than adults at facial recognition, as Nelson and his colleagues discovered nearly a decade ago when they tested babies' ability to discriminate among different human and simian faces. Facial decoding skills develop during the first six months of life, when babies can easily distinguish among human and monkey mugs, a talent that ebbs with time. By nine months, children can still differentiate among human faces but can no longer recognize different monkey faces. As Nelson explains, our facial processing skills depend in part on our experience: The more we're exposed to other people, the better able we are to distinguish between individuals. Unless we regularly hang out with monkeys, we're apt to think they all look alike.

To prove this point, Nelson gave a book of macaque faces to the parents of 13 six-month-olds and asked them to spend a few minutes every day showing their children the faces. Another 13 babies received no macaque training. After three months, the babies who had regularly viewed monkey faces could differentiate between individual monkeys; the control babies could not. The results, says Nelson, "show that our experiences play a huge role in what faces we can and can't recognize." Ongoing studies by Nelson and others analyzing our ability to differentiate faces of other races, ethnicities, and genders suggest similar effects.

More than just cocktail-party fodder, Nelson's findings offer stunning insights into how our visual system develops. Back at the lab, Tommy wears a cap netted with electrodes, which measure how his brain reacts to visual stimuli. As faces bearing exaggerated emotions—joy, sadness, fear—flit across the screen, a computer generates a graph based on his responses. If Tommy's facial processing skills are similar to those of other babies his age, he'll focus the longest on fearful expressions, even though he doesn't yet understand what they mean. Research suggests that babies are typically first attracted to fearful faces and later to expressions of sadness, happiness, and anger. This decoding helps us form relationships and understand each other.

In contrast, babies at high risk for autism—typically those who have an older sibling with the developmental disorder—appear to lack face-reading expertise. "Children and adults with autism tend to avoid looking directly at other people's faces, particularly the eyes," explains Nelson. "If they focus on anything, it's the mouth or the edges of the face." They also don't seem to recognize faces well: When exposed to images of their mother's face or that of a stranger, most children are drawn to Mom's visage. Those at risk for autism, however, respond better to strangers' faces, if they respond at all.

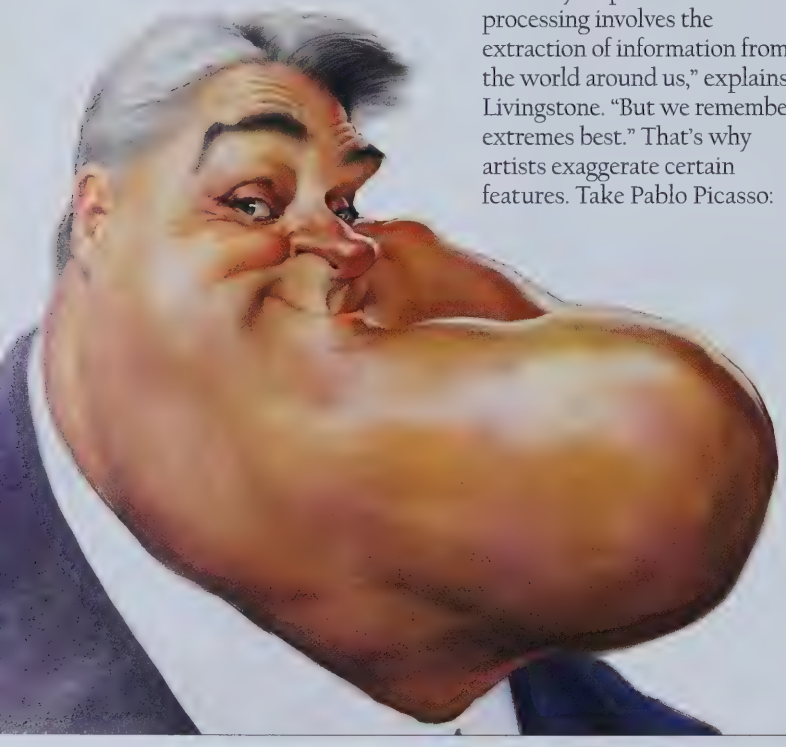
Findings like these may enhance the diagnosis and treatment of autism symptoms. "Our research has the potential to help us identify kids with autism as early as six months," says Nelson; the disorder often isn't diagnosed until the child is at least two years old. "If we can detect it earlier, we can treat it earlier, too."

—Jessica Cerretani

GET THE PICTURE?

We may be more adept at identifying caricatures than faithful portraits

Bob Hope's nose. Angelina Jolie's lips. Jay Leno's chin. For most of us, these features—and the famous faces that frame them—are instantly recognizable. Now, researchers are discovering what cartoonists and other artists have known for years: We are adept at identifying caricatures of faces. In fact, says Margaret Livingstone, an HMS professor of neurobiology, we may be *more* skilled at identifying caricatures of people than photographs of them.

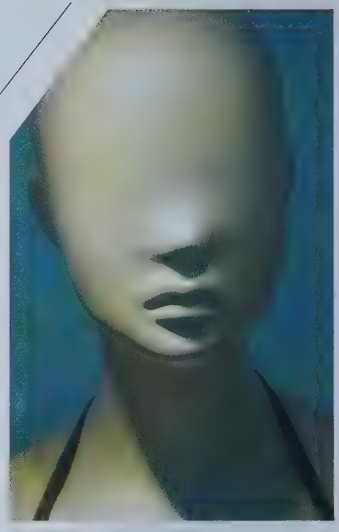


"Every step in visual processing involves the extraction of information from the world around us," explains Livingstone. "But we remember extremes best." That's why artists exaggerate certain features. Take Pablo Picasso: His painting of Gertrude Stein, while abstract, is identifiable to anyone familiar with the writer's wide forehead and strong nose.

There's a scientific basis for this phenomenon. Recently, Livingstone and colleagues used functional magnetic resonance imaging to identify an area of the brain in macaque monkeys called the middle face patch, which consists almost entirely of cells dedicated to face recognition. When the monkeys were presented with a series of real and cartoon faces, their face-selective neurons responded similarly to both. And in nearly half of the cells, cartoon faces elicited the best or second-best response compared to real faces.

The findings, says Livingstone, show that caricatures signal a person's identity through the shape of and the spacing of certain features, like the curve of a mouth or the distance between eyes. "Our cells appear to be attuned to such facial differences," she says. "That's why caricatures work so well."

—Jessica Cerretani



Losing Face

Imagine not being able to recognize your spouse in a crowd of faces or forgetting what your own child looks like. Although this may sound like an episode of *The Twilight Zone*, for some people, such surreal events occur every day. Also known as face blindness, prosopagnosia—the inability to recognize faces—may affect up to 2 percent of the population. Brain injury can trigger face blindness and, for reasons that are unclear, the condition is present in some people from birth.

Research by HMS cognitive neuroscientist Beatrice de Gelder and other investigators is shedding light on this intriguing disorder. One recent study, for example, suggests that smiles, scowls, and other emotional expressions may help prosopagnosics better recognize faces. De Gelder and her colleagues found that emotionally expressive faces activated certain areas in the brains of lifelong prosopagnosics, while neutral faces did not.

"Such findings suggest," de Gelder says, "that emotional information may play an important role in the way we process faces."

—Jessica Cerretani

GAME ON

Virtual spaces may help blind people navigate real ones

Video games aren't just fun time sinks. Research suggests they may help blind people navigate virtual—and possibly real-world—spaces. In a recent study, Lotfi Merabet and Jaime Sanchez, a collaborator from the University of Chile, reviewed research in which blind people played computer games that employed audio cues such as footfalls and door knocks to guide players through a virtual maze. Subjects were then asked to use blocks to re-create the route taken. Their overwhelming success revealed that they had created new cognitive spatial maps. Even more intriguing, functional magnetic resonance imaging of participants' brains showed activity not just in the auditory and sensory-motor regions, but also in areas associated with vision. Merabet, an HMS assistant professor of neurology then with Beth Israel Deaconess Medical Center and now with the Massachusetts Eye and Ear Infirmary, hopes that such games will offer blind people another means of learning to navigate their environments.

WHAT MEETS THE EYE

Our ability to take in visuals may reveal only a small portion of what is really there

Vision, wrote Jonathan Swift, is the art of seeing the invisible. In truth, however, we may not even notice the obvious, says Jeremy Wolfe, HMS professor of ophthalmology and head of Brigham and Women's Hospital's Visual Attention Lab. Together with Todd Horowitz and other colleagues, Wolfe is identifying the ways in which we search for objects and detect changes in what we see—research that has real-world implications for fields as diverse as baggage screening and radiology. The researchers' conclusion: We often miss what's right in front of our eyes. "We believe we're viewing the whole world," explains Wolfe. "But we're only processing a small part of it at any one time."

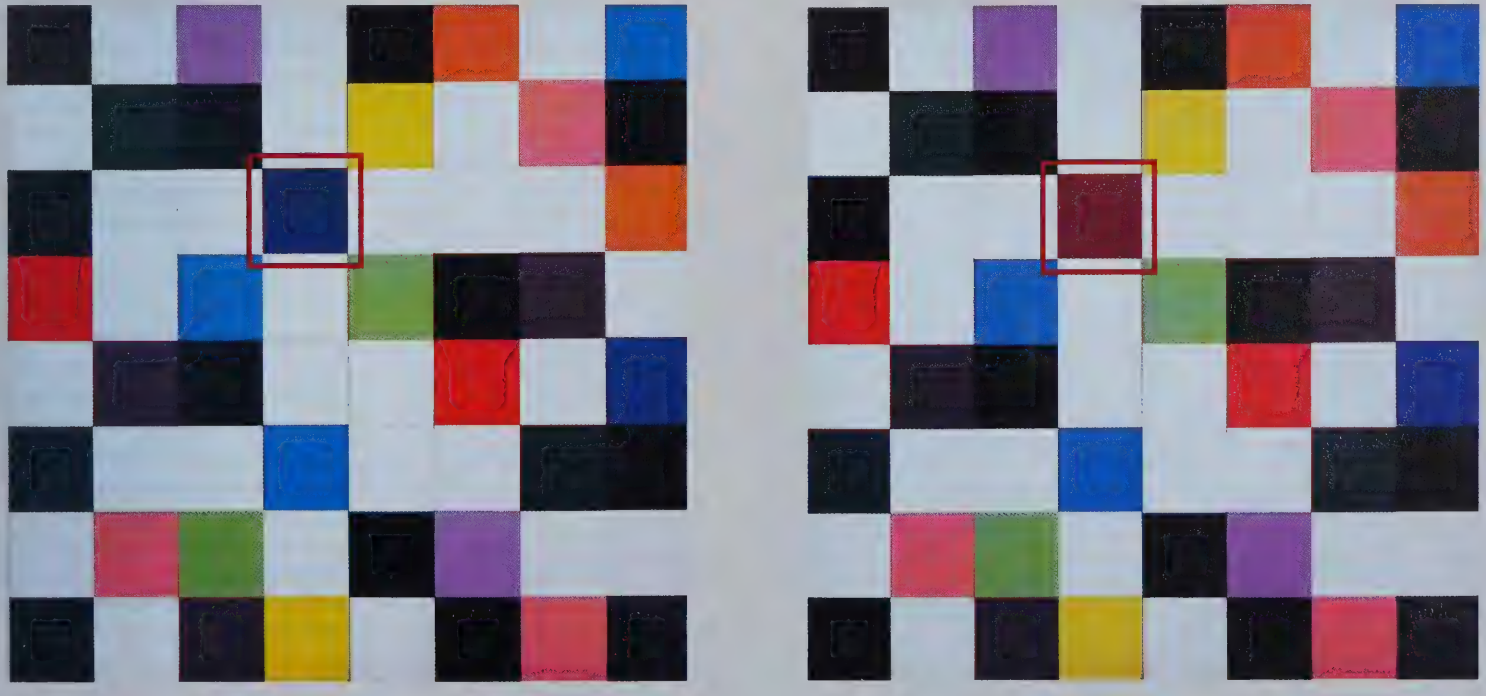
We perform visual searches every day, whether rifling through a drawer for car keys or assembling a jigsaw puzzle. But some searches—for a gun in carry-on baggage or a tumor on an MRI scan—are more crucial than others. Studies by Wolfe, Horowitz, and others suggest that the less common an object is, the harder it is to spot it when it appears. "Targets like guns and tumors are relatively rare," says Horowitz, an HMS assistant professor of ophthalmology. "So we're less likely to notice them when they do show up."

Inspired by findings from their laboratory research, in which volunteers were asked to locate unique letters or symbols on a computer screen—a single letter *T* in a field of *L*s, for example—Wolfe and his colleagues have expanded their experiments. In one recent study, they asked participants to search for weapons in computer-simulated baggage. The participants were told the rough likelihood that a weapon would be present and were rated on both the time it took them to identify the object and their accuracy. When told that weapons were rare, participants dismissed luggage more quickly and failed to locate more of the weapons that were present. When told that the weapons were common, they dismissed luggage more slowly and reported seeing weapons that were not present.

"This phenomenon is likely ancient and widespread rather than a product of modern civilization," Wolfe says. "If a prehistoric ancestor was examining a bush that almost always yielded food, for example, she probably kept searching for a long time."

The vision laboratory's findings have practical applications for training airport security personnel, Wolfe adds. He is planning to conduct similar investigations working with radiologists, who worry about misses as well as the consequences of false-positive reports of tumors. The research may also translate to other types of visual searchers, from Coast Guard officers looking for overturned boats to government employees interpreting spy satellite images.

—Jessica Cerretani



COLLAGE: ELLSWORTH KELLY, COLORS FOR A LARGE WALL, 1951, OIL ON CANVAS, MOUNTED ON 64 JOINED PANELS, 94.5 X 94.5 INCHES (240 X 240 CM), THE MUSEUM OF MODERN ART, NEW YORK. GIFT OF THE ARTIST, 1969; DIGITAL IMAGE © THE MUSEUM OF MODERN ART/LICENSED BY SCALA/ART RESOURCE, NEW YORK

SORRY SIGHT: Jeremy Wolfe and Todd Horowitz use Ellsworth Kelly's *Colors for a Large Wall* to demonstrate a phenomenon known as change blindness: the frequent inability of our visual system to detect alterations to something in plain view. The researchers give viewers three seconds to notice the difference between the images.

SECOND SIGHT

Remarkable research suggests some blind people can "see"

The man made his way down the hallway, maneuvering with ease around the boxes, chairs, and other obstacles. For most people, this act would be routine, one performed countless times each day. This man's journey, however, was anything but ordinary. He circumnavigated the clutter without a misstep—while seeing none of it.

Damage from two strokes had left lesions in both of the man's visual cortices, rendering him blind. Identified only by his initials, TN required a cane and his wife's assistance to walk down the street. His performance in the obstacle course, part of an experiment to assess visual capacities in the blind, stunned investigators.

"We were absolutely shocked by his ability to navigate the corridor," says the study's lead researcher, Beatrice de Gelder, a cognitive neuroscientist at both HMS and Tilburg University in the Netherlands. TN was surprised, too. "He hadn't made any conscious effort to hear or feel his way around," de Gelder explains. "This was all automatic behavior."

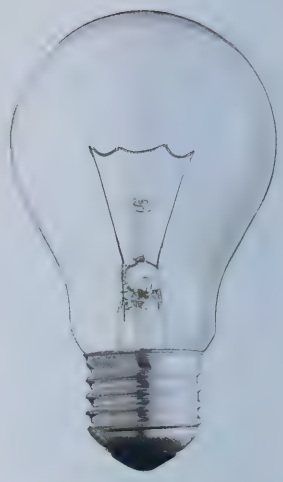
De Gelder's study was the first to show in humans what had been reported previously in monkeys: that we may be able to detect aspects of our environment, even if we aren't aware of seeing them—a concept known as blindsight. The result, says de Gelder, "illustrates in a fairly dramatic way that the brain has a number of alternate routes that can be mobilized when the main avenues to vision are blocked."

That's because retinal cells appear to project images not only to the visual cortex, but also to other parts of the brain related to vision and emotion. For TN and others whose other cognitive functions and eyes remain intact, these areas may still respond to visual cues, allowing them to react to such stimuli, if not actually "see" them.

Blindsight isn't limited to navigational skills. Other research by de Gelder and her colleagues suggests that blind people may be able interpret facial expressions as well. Experiments with TN and other visually impaired people have shown that certain facial expressions—fearfulness, for example—can cause study subjects to cringe or otherwise react, even though they cannot consciously view those expressions.

For de Gelder, who is planning further studies involving TN this year, such findings demonstrate the importance of looking beyond the obvious. "We tend to concentrate on the major visual systems in the brain," she says. "But we may have hidden resources."

—Jessica Cerretani



Risk Assessments

Could the humble light bulb play a role in the development of cancer? That's the implication of a growing body of evidence that links breast cancer risk with exposure to artificial light. Two recent studies led by research associate Erin Flynn-Evans and her colleagues at the Division of Sleep Medicine at Brigham and Women's Hospital provide further insight. The first study looked at 1,392 blind women with either little or no ability to perceive light; 66 had been diagnosed with breast cancer. After controlling for other risk factors, the researchers found that women with no light perception had a more than 50 percent reduction in breast cancer risk compared to those who could see some light.

A related study showed that the women with no light perception had their first menstrual period at a younger age than those with some light perception. The findings were surprising, Evans says, since earlier menarche is associated with *increased* odds of breast cancer in sighted women. Taken together, these findings suggest that reproductive differences aren't responsible for the lower breast cancer risk observed in blind women. Further research is needed on the effects of artificial light on cancer development.

—Jessica Cerretani

PHOTOS: STOCKBYTE/GETTY IMAGES; KICK IMAGES/ISTOCK EXCLUSIVE/GETTY IMAGES

VISION QUEST HMS discoveries have helped shape our vision of the future

1950 More than half a century ago, famed retinal surgeon Charles Schepens saw the need for a research organization dedicated to exploring new treatments for incurable eye disorders. Originally called the Retina Foundation, the HMS affiliate has since been renamed the Schepens Eye Research Institute for its founder. Its researchers have published nearly 5,000 scientific papers and books about health and eye disease.

1959 Glimpses into a cat's eye shed light on the way nerve cells respond to light, motion, depth, color, and other visual stimuli. With their studies of the feline visual system, David Hubel and Torsten Wiesel, both researchers in the then-new HMS Department of Neurobiology, laid the foundation for the field of visual neurophysiology and greatly expanded knowledge of sensory processing. Their work was recognized with the 1981 Nobel Prize in Physiology or Medicine.

1965 When Lloyd M. Aiello, now an HMS clinical professor of ophthalmology, began treating patients blinded by diabetic retinopathy, his waiting room was filled with seeing-eye dogs—many of which outlived their owners. Now, the vast majority of people with the disease retain their vision, thanks to Aiello's pioneering work. With his late father-in-law, he pioneered pan-retinal coagulation, a treatment that uses a laser to halt the sight-stealing proliferation of blood vessels in people with diabetes.

1992 Thousands of patients have avoided blindness thanks to FDA approval of the Boston Keratoprosthesis, an artificial cornea developed by Claes Dohlman, former chief of ophthalmology at the Massachusetts Eye and Ear Infirmary. His invention is used in people with severely diseased corneas when transplants from human donors fail.

1994 Like father, like son: A third-generation ophthalmologist at Joslin Diabetes Center and HMS, Lloyd P. Aiello has spearheaded his own research into the roots of vision loss. His studies have shown that vascular endothelial growth factor, or VEGF, plays a major role in the proliferation of blood vessels in eye diseases including diabetic retinopathy and age-related macular degeneration.

2000 Age-related macular degeneration is still the leading cause of blindness in older adults, but its treatment has improved over the years, thanks in part to the efforts of Joan Miller '84, chief of ophthalmology at the Massachusetts Eye and Ear Infirmary. Along with her colleague Evangelos Gragoudas, she pioneered the use of photodynamic therapy to damage abnormal blood vessels in the eye without harming the retina. This approach, which was approved in 2000 as the first treatment for age-related macular degeneration, has reduced vision loss in many patients.

2006 The rich legacy of angiogenesis pioneer Judah Folkman '57 has not been limited to cancer treatment. Research by the late investigator and others at Children's Hospital Boston led to the creation of the anti-VEGF drug ranibizumab for the treatment of age-related macular degeneration. The FDA approved the medication after data showed that it might not only slow vision loss but also restore sight in some patients.

2010 Once the stuff of science fiction, a bionic eye is closer than ever to becoming reality, courtesy of researchers at the Boston Retinal Implant Project—a joint effort of the Massachusetts Eye and Ear Infirmary, the Veterans Affairs Boston Healthcare System, and the Massachusetts Institute of Technology and co-founded by HMS Associate Professor of Ophthalmology Joseph Rizzo III. The device would require users to wear a small camera mounted to eyeglasses. The camera would transmit signals to a surgically implanted chip behind the retina, helping people with macular degeneration or retinitis pigmentosa regain some vision.

VIEW FINDER: Most people with diabetic retinopathy retain their vision thanks to the pioneering work of Lloyd M. Aiello and collaborators.

PHOTO: JOSLIN DIABETES CENTER

ILLUSTRATION: SCOTT LAUMANN

the Sounds of Silence

by SANJAY GULATI

Modern neurobiology suggests that the human senses are more numerous than the five Aristotle identified. They are also less distinct; they overlap and intertwine.

Lip readers like me, for example, experience *seeing* as *hearing*. My mind creates a voice for everyone I meet. I once "heard" the high, melodic voice of a woman until I realized that she was actually male, and the voice I had imagined dropped an octave. On another occasion, I finally caught the word "London" on the lips of a young scientist with whom I had been struggling to converse. The word triggered a mental filtering; when I reassigned him a British accent and diction, he was instantly audible.

he motion of lips, and the dance of expressive hands

Sound is *not* language. Even when hearing aids provide some sound, children may fail to master a language.

I came to lip reading relatively late. I began losing my hearing in late childhood; by early adulthood, I was deaf. And although my musical training has stayed with me—I can play a symphony in my head or a fugue on the piano—my perception of physical, linguistic, and social space has changed remarkably.

Perception of body language, for example, has replaced perception of intonation. And an acute awareness of vibrations has replaced hearing through walls. We all respond to the feel of sound. Deaf people sometimes hold balloons while dancing at parties, as the light vibrations of the balloons transmit the music's bass line and beat. Physical vibrations, in fact, can often be heard. Aspirated consonants produce an audible puff of air; the *p* in s*p*ot, for example, as compared with that in sto*p*. Remarkably, a puff of air felt on the back of the hand can make listeners perceive an unaspirated consonant as aspirated.

At the same time, what I *see* can change what I *think* I hear. I learned American Sign Language as an adult, so my mind still gives lip reading priority over signing. I can be blind to perfectly clear sign language when I see a different word on a speaker's lips. The more readily I can predict a speaker's words, of course, the better I will hear them. "Paper or plastic?" is easy to catch at the cash register. The frustrating corollary is that the most interesting information is always the most difficult to hear—I'll hear a joke but miss its punch line.

Despite these new perceptions, I still compose a soundtrack for life, imagining footfalls, a teakettle's whistle, even road noises while driving.

Listening to Reason

Real hearing exists on a continuum, from the supernormal hearing of many children and musicians, through the many degrees of hearing impairment and deafness, to the rare cases in which hearing is entirely absent. While a deaf person's broken ears can seem tragic to hearing people, a nonsigning person's inexpressive hands can seem just as lamentable to signers.

For hearing people, the acquisition of language is effortless and its ongoing use largely unconscious. As a result, a dividing line seems to fall somewhere at the level of being able to use the telephone and to make dinner-table conversation; those with hearing above that line are often unkind to those with hearing below.

That attitude can sometimes soften. I serve as a consultant psychiatrist to the American School for the Deaf. In its surrounding community of West Hartford, Connecticut, the culture has shifted toward inclusivity. Instead of floundering in discomfort, local restaurant and store employees communicate flexibly with deaf customers, writing on tablecloths, engaging in rudimentary sign language, and accepting some awkwardness. There, the deaf person feels *invited* to belong to society. Disability does not inhere within the body, after all; it is created equally by physical status and societal response.

Marginalization within society is a potential loss for people without hearing, yet some deaf people experience a deficit even more profound. The most disturbing symptom among the deaf patients in my psychiatric practice, and the focus of my research, is language dysfluency caused by language deprivation. Children learn sign languages early, as they do spoken ones, with a nearly complete comprehension of grammar by age three. Those not exposed to usable language by the age of four will never learn any language fluently. And a child with no exposure by seven or eight will acquire a form of mental retardation.

Sound is *not* language. We know little about how our innate capacity for language allows us to transform into linguistic beings. Even when hearing aids or cochlear implants provide some sound, children may fail to master a language. They can be deprived of language when early intervention services are skimpy, when educational methods fail, or when grieving parents cannot bring themselves to learn sign language. Whatever the reason, the result is heartbreaking.

A young deaf man who had not been exposed to sign language until age nine once signed to me, "That in a you know people me deaf same want want that you know stay family love lost communication fail." Straining, my interpreter and I guessed that he was saying that, for ease of communication, he would rather live in a group home with other deaf people than with his family, whom he loved. Nonsigning observers might mistakenly believe that he was signing fluently. Psychiatrists unfamiliar with language deprivation might misdiagnose him as psychotic or cognitively impaired. His lack of language had shattered his life.

In less severe cases, language deprivation results in diminished fluency. Deaf adolescents may sign like children, and their achievements as adults may be vastly compromised. Language deprivation also correlates dramatically with aggression and self-injury. Deprived children may lash out when they can neither communicate their feelings in words nor manage those feelings internally through language.

Lending an Ear

I had loved music and spoken language so much while growing up that I could never have predicted how I would feel about deafness. But my experience confirms what linguists have found—that sign languages, often the most natural forms of communication for deaf people, are the equals of spoken. My experience also confirms what disability advocates contend: that "health" and happiness are not the same.

The hard-of-hearing me cranked my hearing aids to full volume, trained my eyes on the speaker's mouth, and gamely guessed at the words. The deaf me has shed hearing devices, experiences an expanded peripheral vision, and reads the light and joyous dance of signing hands.

There are many ways to hear. One can hear a singer's voice, pure and soaring in an auditorium. One can hear a speaker's animated mouth. Or one can hear a signer's blessedly evocative hands. Metaphorically, hearing is about attending to and understanding one another. Those with sound still have much to learn about listening to the deaf.

Sanjay Gulati, MD, is an HMS instructor in psychiatry. He serves as a child psychiatrist for both the Deaf and Hard of Hearing Service at the Cambridge Health Alliance and the Deaf and Hard of Hearing Program at Children's Hospital Boston.

GOING GAGA: Although the flash and sparkle of pop star Lady Gaga may dazzle, the frazzle to auditory structures caused by the ear-splitting volume of rock concerts may provide the more lasting memory.

PHOTO: DARRIN ZAMMIT LUPI/REUTERS/CORBIS

THE DANGERS OF A MISSPENT YOUTH

Researchers uncover the crescendoing costs of noise exposure

Lady Gaga mounts the stage in a sequin-studded corset and grabs the mike. Bleached-blonde bangs hide her eyes; short black boots accentuate long, bare legs. She pauses briefly before a spray of pyrotechnics and an explosion of drums send her hips gyrating. With a gloved fist pump, the high-kitsch diva begins belting out the opening verse to "LoveGame." Teen nirvana.

That night, a young fan returns home with dreams of life as a pop phenomenon—and ringing ears. By the next day, though, her hearing returns to normal, and the impact of her evening of auditory excess has begun to fade, or so it seems. Research now suggests that ears hold grudges: Damage may progress for months, even years, after an assault.

"Until recently, we accepted the dogma that noise has a time-limited effect," says Sharon Kujawa, HMS associate professor of otology and laryngology and director of audiology at the Massachusetts Eye and Ear Infirmary (MEEI). "We assumed that ongoing changes were related to other causes—to aging, for example. We also assumed that the return of hearing thresholds in the hours and days after exposure signaled a recovered ear." Studies by Kujawa and colleagues are now challenging such assumptions about noise-induced hearing loss—and promising to inform future treatments.

The need for such treatments is growing. In the United States, an estimated ten million people have permanent hearing loss from noise, other forms of trauma, and aging. New work shows that hearing loss is a growing problem in young adults, and noise exposure is the primary suspect.

Kujawa collaborates with M. Charles Liberman, the Harold F. Schuknecht Professor of Otology and Laryngology at MEEI, to probe the relationship between noise-induced and age-related hearing loss, processes long assumed to be simply additive in a given ear. These investigators made a surprising discovery when they monitored genetically identical adult mice for years after subjecting them to loud sounds. Fleeting auditory insults—roughly akin to a blaring rock concert—changed the way the animals' ears aged, long after the noise had stopped.

Additional research has since provided a possible explanation for these observations. Kujawa and Liberman have detected changes in cellular elements that convey messages from the sensory receptors of the inner ear—the hair cells—to the auditory nerve and brain. The animals still had picture-perfect hair cells, but shortly after noise exposure, the ability of those cells to communicate with the auditory neurons was interrupted—first by loss of structures that store and release chemical messengers called neurotransmitters, next by loss of the spindly extensions of neurons that reach the hair cells, and finally, over months to years, by loss of the auditory neurons themselves.

"These mice could still detect soft sounds in a quiet setting," says Kujawa, "but they lost processing power. Translating to humans, they might hear you, but not understand you."

In people, processing power comes in handy when we need to sort specific sounds from a jumble surrounding us. Kujawa suspects that processing deficits exacerbate other hearing problems, including those related to aging. Perhaps the teen concertgoer will pay for her exposure in a few decades, when a full complement of auditory neurons would have helped her understand the conversations of friends in a noisy restaurant.

Prevention in the form of ear protection is key. But even when protection is available, life does not always allow time for it. An improvised explosive device, for example, could detonate near soldiers, leaving them with permanent threshold shift, which impairs communication and changes the quality of their lives forever. What would Kujawa's findings mean for them?

"Researchers at Harvard and around the world are working to develop drugs that could be administered before exposure to protect the ears or after exposure to rescue the ears and preserve hearing," says Kujawa. "The goal is to interfere with the processes that destroy auditory neurons and demolish delicate hair cells."

A morning-after pill for your ears. Imagine the possibilities.

—Alyssa Kneller

MUSICAL MEDICINE

Melodies can help heal disharmonies in speech

A lesion on the elderly man's left frontal lobe, damage from a massive stroke, has robbed him of the ability to speak. The clinician sitting opposite him asks him to repeat a simple phrase: "Happy birthday to you." The man struggles, but only manages, "En oh en oh en oh."

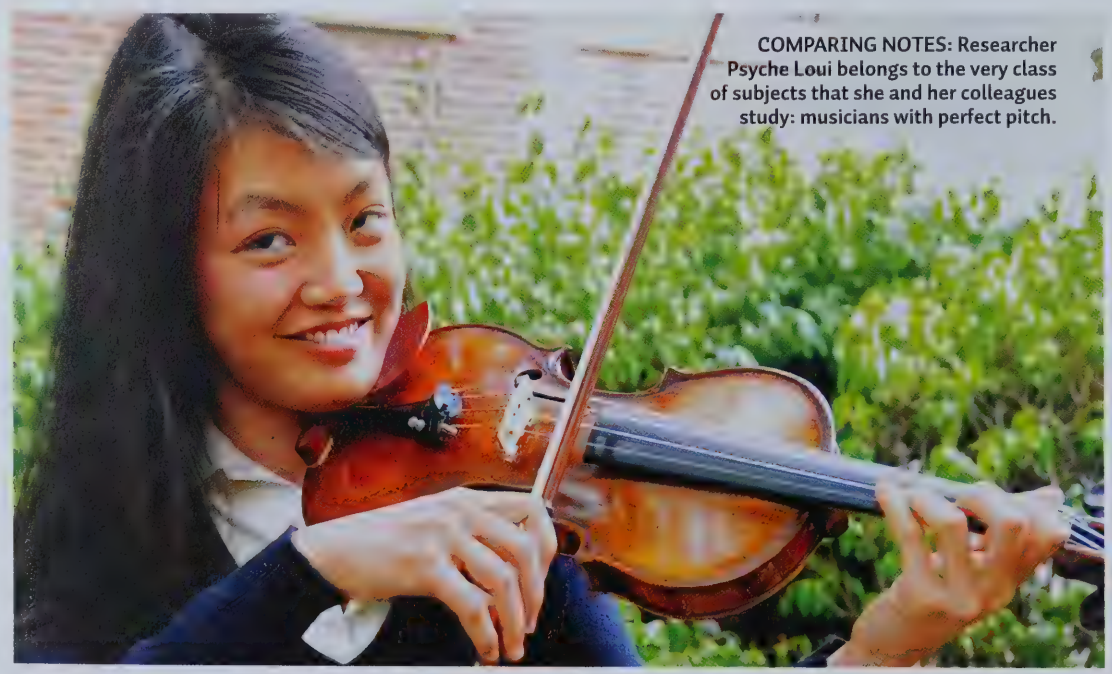
The clinician then asks him to sing the phrase. Holding his left hand, moving it rhythmically, she initiates the song. After a few attempts, she's silent, and he sings it as clearly as anyone carrying a cake with lit candles. The clinician then asks him, again, to *speak* the phrase. Without a hitch, he repeats, "Happy birthday to you."

In less than two minutes, an extraordinary feat has occurred. Yet for researchers like Gottfried Schlaug, HMS associate professor of neurology and director of the Music, Neuroimaging and Stroke Recovery Laboratories at Beth Israel Deaconess Medical Center (BIDMC), such events aren't new. Medical literature going back a century describes stroke victims who have regained aspects of speech through melodic intonation therapy. "The difference," Schlaug says, "is that now we have the neuroimaging tools to investigate what occurs in the brains of people who relearn language through song."

These tools reveal substantial overlap between areas of the brain that process music and language. Damage to the left hemisphere significantly impairs speech. And although the right hemisphere has some capacity for language, it responds best to clearly structured information, such as melodies. Layering language over melodies engages the right hemisphere's latent language capacity.

Schlaug speculates that when people cycle between singing and speaking, the melodic contour and continuous voicing enable the right hemisphere to vocalize words and phrases, creating a kind of language-smuggling Trojan horse. By moving the elderly man's left hand, the clinician helps him connect sounds to actions, sketching auditory motor maps into the right side. If a patient rehearses this entire process long enough, the brain's right side eventually compensates for the impaired left—and even changes structure. "Ultimately," Schlaug says, "we trick the right hemisphere into learning how to speak."

Neurologists once embraced the theory that the right hemisphere of the brain housed a person's creativity, while the left hemisphere processed information such as math. Musicians, then, should be highly right brain lateralized. In the early 1990s, Schlaug tested that theory. Using MRI technology to scan the brains of both musicians and nonmusicians, he and his colleagues discovered that the brains' morphologies revealed the opposite. Musicians, on average, were more left brained; those with perfect pitch were the most left brained of all.



COMPARING NOTES: Researcher Psyche Loui belongs to the very class of subjects that she and her colleagues study: musicians with perfect pitch.

PHOTO: BRUCE WAHL/BETH ISRAEL DEACONESS MEDICAL CENTER

Schlaug has since focused on the planum temporale, which is part of the auditory cortex. The planum temporale has a more pronounced leftward asymmetry in musicians with perfect pitch than in musicians without perfect pitch and in nonmusicians.

"Professional musicians practice their skills many hours a day, for many years," says Schlaug. "We think of musicians as auditory-motor athletes whose long-term training has an effect on brain function and structure."

These findings launched Schlaug onto a trajectory of collaborations with researchers such as Psyche Loui, an HMS instructor in neurology at BIDMC and a violinist with perfect pitch, and David Alsop, a musician who is also an HMS associate professor of radiology at BIDMC.

As Schlaug, Loui, Alsop, and colleagues use the latest imaging technologies to study the brains of musicians and nonmusicians, the unanswered questions mount. How, for example, does music affect brain adaptation, reorganization, and even plasticity? The team is also in the last phases of a longitudinal study on the neurobiological effects on children of learning to play an instrument.

And finally, what about professional musicians? Schlaug suspects they are not born with the natural advantage of an auditory-motor system that enables them to play a musical instrument. Instead, given the plasticity of the brain, particularly at a young age, their continued musical practice likely leads to brain changes that can be detected by modern imaging techniques. For many of us this is good news. "Unless you're tone-deaf," Loui says, "you probably have some unconscious musical abilities even if you can't sing in tune."

—David Cameron

PHOTO: FREDERIC CIROU/PHOTOALTO RF COLLECTIONS/GETTY IMAGES

MISGUIDED BY VOICES

Auditory hallucinations light up the brain

For weeks now, she'd been feeling that things weren't *quite* right. Nothing she could put her finger on, just a low-grade suspicion that everyone around her was merely trying to act natural. When her doctor scheduled routine blood work, she could barely quell the nausea of foreboding. And when the clinic's seemingly harmless phlebotomy tech asked her to make a fist so he could prod her forearm for a vein, the queasy dread in her stomach bloomed.

Then she heard them—a fluttering of voices, hushed, secretive, drifting from the air vent in the ceiling.

"We should do it now," one of the voices whispered.

"Yes," hissed another. "She's right here. Let's do it."

The tech turned, syringe in hand, and suddenly her qualms made sense: She was at the center of an elaborate medical experiment. And everyone in the clinic was in on it.

She bolted.

This woman's experience typifies what people—usually those suffering from schizophrenia—report when describing auditory hallucinations. Such people can pinpoint where the voices are coming from and whether they sound male or female. The voices are always hostile.

Yet according to Dost Öngür, an HMS assistant professor in psychiatry at McLean Hospital, just because it's a hallucination doesn't mean it's a delusion.

"These patients actually hear something," he explains. "They don't just imagine voices; their auditory circuits are fully engaged. All that's missing is the external stimulus."

Brain scans confirm this statement. David Silbersweig, chair of the Department of Psychiatry at Brigham and Women's Hospital, and others have found that when patients experience auditory hallucinations, their primary auditory cortex, the region of the brain that receives direct input from the ears, is fully activated. Yet the brain's anterior cingulate cortex, which differentiates between external and internal stimuli, loses its ability to make that distinction. In fact, postmortem analyses of patients often show cellular abnormalities in that very brain region.

"It's a twofold mechanism," says Öngür, who conducts brain imaging studies as part of his work as clinical director of McLean's Schizophrenia and Bipolar Disorder Program. Öngür adds that the origins of auditory hallucinations are unclear. Very likely, abnormalities occur in the brain during key moments of early development, and these abnormalities make it difficult for patients to meet the demands of daily life, ultimately leading to symptoms. For now, clinicians can treat those symptoms with drugs that regulate dopamine activity, but such treatments don't address the source.

"I wish we knew what caused these hallucinations," Öngür says. "I'm hopeful that our research will soon provide more clues."

—David Cameron

Ear Splitting

When you're in a restaurant with music blaring overhead and juicy gossip the next table over, it's easy to zone out on your immediate conversation.

That capacity to tune in—or tune out—a single sound in a noisy room is called selective auditory attention. Seung-Schik Yoo, an HMS associate professor of radiology at Brigham and Women's Hospital, and his colleagues recently studied this ability in hopes of determining how much control individuals can exert over their own brains.

In two small studies, the researchers found that, with the help of nearly instantaneous biofeedback, participants learned to listen better—or at least to boost activity in the auditory portion of their brains, a skill they retained for about two weeks.

For the studies, participants lay in MRI machines and listened to sounds while wearing special goggles that displayed real-time data of their brain activity. Most people who received correct neurofeedback were able to increase their short-term ability to activate the brain's auditory areas. In contrast, the control group, thwarted by the random feedback from their goggles, failed to achieve a similar boost.

Yoo believes these findings hold promise for developing noninvasive ways to improve brain function and to overcome brain damage and certain neurological diseases. Yoo is now developing a new noninvasive method to precisely and selectively stimulate or suppress activity in targeted regions of the brain as small as a grain of rice.

"We have the innate ability," he says, "to activate our brains."

—Carol Cruzan Morton

BACK FROM THE DEAD

Sound progress is being made in efforts to regenerate sensory cells

Hearing aids and cochlear implants bring sound into the lives of many with hearing loss. Both devices compensate for missing hair cells and auditory neurons, the delicate structures of the inner ear that receive, amplify, and translate sound into electrical signals to be processed by the brain. But these devices treat the symptoms of the loss, not the cause.

Researchers at the Massachusetts Eye and Ear Infirmary (MEEI) and the Harvard Stem Cell Institute hope to offer patients another treatment option—drug cocktails that coax the inner ear into growing new sensory cells. Albert Edge, an HMS associate professor of otology and laryngology at MEEI, and his colleagues study adult stem cells of the cochlea. Although these cells initially divide and transform into sensory cells, by puberty they become inactive.

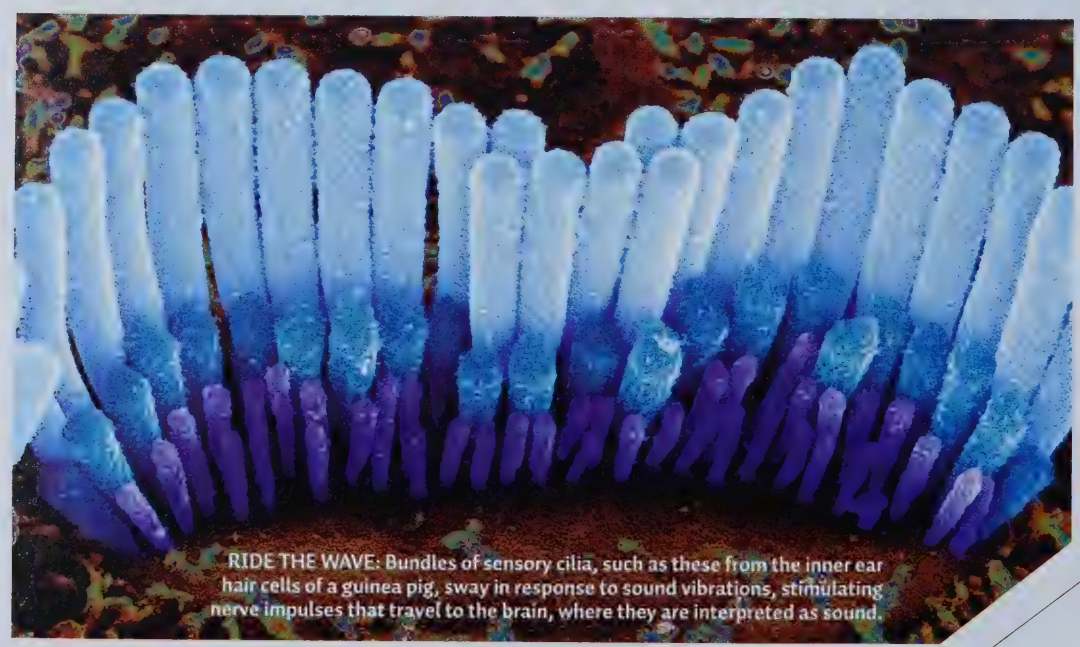
Edge's team maps the process by which these stem cells develop specific functions, identifying factors that push them toward particular fates. The Edge lab and other groups have discovered, for example, that activation of the transcription factor Atoh1 transforms cochlear stem cells into hair cells. Working at the Harvard NeuroDiscovery Center, Edge's team applied more than 100,000 chemicals one by one to cell colonies and identified roughly a hundred that boost Atoh1 levels. Next, they must validate the findings in cochlear stem cells.

"Our ultimate goal is to identify chemicals that will activate patients' endogenous stem cells," says Edge. "We may need to administer a series of compounds to the inner ear to achieve this result."

That effort would also require sophisticated vehicles for delivering drugs to the cochlea, which hides behind a blood-perilymph barrier. Led by Michael McKenna of MEEI and Jeffrey Borenstein of MIT and Draper Laboratory, a team of auditory scientists and engineers—including Sharon Kujawa and William Sewell, both HMS associate professors at MEEI—has created one possible candidate. Working in guinea pigs, the researchers are developing a remote-controlled device that sits behind the ear in the mastoid cavity and stores drugs in a reservoir. At the press of a button, the device releases the drugs, which travel through a tube that winds from the middle ear into the cochlea.

"We can use this device to infuse the inner ear with drugs that prevent the degeneration of sensory cells," says McKenna, an HMS professor of otology and laryngology. "After we learn more about the endogenous stem cells, we can tackle those too."

—Alyssa Kneller



RIDE THE WAVE: Bundles of sensory cilia, such as these from the inner ear hair cells of a guinea pig, sway in response to sound vibrations, stimulating nerve impulses that travel to the brain, where they are interpreted as sound.

Listen to This

A yipping dog, a whistling teakettle, a thunderclap. You would think it would be easy to recall hearing such sounds 15 minutes later—but it's not.

"People simply aren't good at remembering sounds," says Todd Horowitz, an HMS assistant professor of ophthalmology at Brigham and Women's Hospital. Horowitz and his colleague, Jeremy Wolfe, an HMS professor of ophthalmology, recently reported on the inferiority of auditory recognition relative to visual recognition.

For several decades, they and other researchers have documented how people remember visual scenes amazingly well, routinely scoring 90 percent or higher when asked to identify previously seen images in a rapid succession of thousands of pictures. But the same is not true with sound. In one of the first studies of its kind, people had difficulty remembering which sounds they had recently heard, whether spoken words, music, or complex auditory scenarios, such as pool-hall conversations. "The most memorable sounds we could find," Wolfe says, "were equivalent to the lousiest pictures."

The consistently lower memory for sounds led researchers to conclude that the brain processes sights and sounds in fundamentally different ways. The team is following up with a study of trained musicians.

—Carol Cruzan Morton

PHOTOS: DR. DAVID FURNESS/WELLCOME IMAGES; ERIC ISSELÉE/ISTOCKPHOTO.COM

MUSICAL NOTES ON HEALING

Mozart promotes health as well as happiness

CLAUDIUS CONRAD

The effervescence of Mozart's piano sonatas delights the ear. Evidence now suggests these works may also soothe the psyche—and even support healing. A recent study by Claudius Conrad, a senior surgical resident at Massachusetts General Hospital, randomized postsurgical critically ill intensive-care patients and had them listen to recordings of gentle Mozart piano music for one hour, during which their sedation was lifted. The control group was not exposed to music, but wore headphones to keep the research team and nursing staff blinded as to whether music was being played.

When Conrad and his colleagues tested the patients, they found that classical music reduced blood pressure and heart rate, lowered stress-hormone levels, and reduced the need for sedatives. Another finding was more surprising: The patients' levels of pituitary growth hormone rose by 50 percent, while levels of interleukin-6, which increases in response to stress, dropped significantly. These changes illustrate the potential of music to encourage relaxation and modulate immunity.

Conrad is well positioned to study the effects of music on health. A concert pianist who trained at conservatories in Bavaria, Germany, he holds not only a medical degree and a doctorate in stem cell biology, but a doctorate in music philosophy as well. His experiences have spurred research into music's effects on another population: surgeons. In a 2009 study, Conrad tested eight expert surgeons on their speed and accuracy while performing computer-simulated laparoscopic procedures and listening to Mozart, to silence, or to the cacophony of simultaneous German folk music and so-called death metal. He found that, compared with silence, the discordant music slowed the surgeons' speed in completing their tasks. Classical music, however, seemed to improve their efficiency.

Like many surgeons, Conrad provides his own soundtrack for the operating room. While his playlist contains a few surprises—European techno rap, anyone?—his favorites remain classical pieces. Surgery, he explains, is not unlike a symphony.

—Jessica Cerretani

Running the Scales

In Gil Alterovitz's ideal world, every operating room is a concert hall, every cancerous tumor a song. Work by Alterovitz, a researcher at the Harvard–MIT Health Sciences and Technology Division and the Children's Hospital Informatics Program, now may make that vision a reality. He and his colleagues have created technology that translates the body's gene expression into music.

The concept first came to Alterovitz in 1998, when his research on how physicians respond to the sensory overload produced by the noise from monitors and other machines in clinics revealed that many physicians had learned to ignore critical alarms—or worse, chose to turn them off.

What would happen, Alterovitz wondered, if all those beeps, buzzes, and bells were replaced with the sounds of violins, violas, and other instruments? In many operating rooms, surgical teams play recordings of everything from classical concertos to classic rock as a way to relax and focus. With this in mind, Alterovitz and colleagues developed a computer program, to be used in laboratories, that translates gene expression—the process by which a gene's DNA sequence is converted to a protein or other product—into music. First, they shrank data from thousands of genes down to four combinations that they believe represent nearly all the data's variability. Next, the researchers assigned each combination a musical note that, when added to other notes, formed chords and then music. Healthy gene networks result in harmonious music—and a pleasing background noise for physicians. But when the genes' behavior reflects disease or changes in bodily functions, the soothing tunes strike a disquieting chord. That jarring change is enough, Alterovitz hopes, to alert doctors to potential problems.

"Colon cancer," he points out, "sounds kind of eerie."

—Jessica Cerretani

PHOTO: C. J. GUNTHER

catching the bouquet

A wine connoisseur follows his nose to diagnose disease. ~ *by* MICHAEL A. LACOMBE

ILLUSTRATION: TOBI NEWSOME

This is how it would work. I would ask the residents to page me whenever they had a case of *Pseudomonas* pneumonia or *Clostridium difficile* enteritis. I might then reward them—or at least those who saw it as a reward—with some brief bedside teaching on the slightly-turned-red-grape odor of *Pseudomonas* or the more intricate coal-tar-in-the-horse-barn smell of *Clostridium*. By keeping the nurses in the operating rooms and endoscopy suites well-supplied with bagels and donuts, I could guarantee a page when gas gangrene or shigellosis appeared, and eventually, merely by sticking my head in the door, I could catch the whiff of rotten apples or rancid butter, nod my head, and wink.

For the more arcane stuff, greater rewards were necessary: a bottle of wine, dinner for two, that sort of thing. Those rewards I posted in the newborn nursery, for example, or on the pediatrics ward. And so I could collect the wet-mouse smell of phenylketonuria, the sweet aroma of maple-syrup-urine-disease, the subtle halibut-gone-bad hint in tyrosinemia. This was great fun at first, as are all hobbies, but in time became a curse, as do most compulsions. Let me start from the beginning.

As an intern, I had an interest in wine. My colleagues knew of my pastime and would often ask for recommendations. I'd steer them toward an affordable Vouvray rather than the pricier Pouilly-Fuissé. From this began a wine co-op. With thirty or so residents interested in an inexpensive mixed case of wine every month, I began a wonderful relationship with the owner of a major wine

our noses are wired to our limbic systems, which are somehow connected to prom nights and fine wines.

store in Rochester, New York. Buying thirty cases of wine every month made me one of his best customers, got me invited to after-hours back-room tastings with heavy hitters from the local high-tech industries, and exposed me to the smell and taste of an incredible array of wines.

It was during those tastings that I realized I had an unusually strong olfactory memory. It wasn't just that I nailed the cedar-pencil whiffs and cigar-box hints amid the roasted cherries of a Pauillac. I remembered those smells, as you might remember a song at your high school prom. And just as you might recall from hearing the melody of that song whom you danced with and what you wore, the whiff of a '61 Pichon-Lalande conjured up all the memories associated with my savoring of it because, as neuroscientists will tell you, our noses are wired to our limbic systems, which are somehow connected to prom nights and fine wines.

Many of those high-tech executives envied my talent. In wine tasting, such a flair is associated with connoisseurs and bon vivants. In medicine, though, anyone who strolls through an endoscopy suite leading with his nostrils is merely considered strange. In both cases, it is a gift—no more than that. Some are born with it.

I began collecting wines and eventually drifted toward cheeses and their smells and tastes, filling the house with the stenches my wife ascribed to Époisses and Livarot. And I planned vacations, holidays, and weekends around aromas I hoped to collect. I heavily lobbied, for example, for a trip to China, ostensibly to see the Great Wall, but with a secret side trip to Xing'an County, which had a problem with typhoid. I needed the disease's freshly-baked-black-bread odor for my collection. Similarly, Brazil could be lovely at a certain time of year, and if my wife could be happy with Rio's shops, I could explore the butcher-shop smells of Brasilia's yellow fever epidemic. (Sadly, not the charcuterie aromas of those wonderful Parisian shops, but rather the off-putting ripeness of the back streets of Chinatown.) My wife put up with these odoriferous escapades. But I was creating a monster of greater proportion.

My monster had to do with my limbic-system connections. I found myself avoiding bakeries heavily into sourdough bread, and then, by association, all bakeries, because of the memories of those kids with pellagra in that orphanage in Casablanca. Eastern European restaurants also made the must-avoid index, as the cooked cabbage conjured up hypermethioninemia. And garlic-laden Italian restaurants were too reminiscent of that awful case of arsenic poisoning in northern Maine.

By then, too, my wife had become suspicious of any travel suggestion. She soon wearied of bland Irish meat-and-potatoes pubs. I longed for a wheel of Brie but couldn't bear another conjured-up image of abscess.

It was with this heavy burden that I found myself on rounds one day. The interns and their attending had summoned me to weigh in on a case that had baffled them all. I was old, they hinted, and had seen everything. Could I render an opinion?

I introduced myself to the patient, a sweet, elderly woman redolent of Chanel No. 5. "I'm a cardiologist," I told her, "but I understand there's nothing wrong with your heart. It's just that your doctors have asked me to see you. I'm old. I've seen everything."

"I've consulted so many doctors, had so many tests," she whined. "Maybe I should go to Boston. Should I go to Boston?" Then she stopped and asked, "What are you looking for?"

"The paperwhites. I smell paperwhites."

"Oh, my daughter threw them out yesterday. What's wrong with me?"

I hadn't a clue. I had read her chart, run through her history. I took another history. Nothing new to add. I asked all the standard questions meant to uncover odd details—occupational exposures, travel, herbal medicines, hobbies. She hadn't worked in any silos, hadn't visited Paraguay, didn't own a parrot. She began to regard me in the way those endoscopy-suite patients inevitably did.

I began the physical exam by taking her hands in mine. I scrutinized her fingernails, scanning them for diagnostic clues. No Muehrcke's lines, no Terry's nails. No hint of disease from her skin. I peered into the pale web of her hair, at her scalp. She pulled away.

"What are you doing?" she asked anxiously. "What are you looking for?"

I didn't know, exactly. I was stalling. I began to examine her heart, listening at the base, then rolled her on her left side to listen at the apex, leaning over her, closer, closer still.

"You're smiling," she said. "Why are you smiling? Did you hear something?"

"What's that smell?" I answered.

Michael A. LaCombe '68 is a cardiologist at Maine General Medical Center. The University of Maine Press recently published his latest book, Bedside: The Art of Medicine, *a collection of fictional medical stories. Unlike those stories, this original essay is excruciatingly factual, as his wife can attest.*

SILENT WITNESS: A Cambodian man views skulls of Khmer Rouge victims killed in the genocide that took place in his country during the 1970s. Many who survived that period suffer panic attacks triggered by smells that recall atrocities they witnessed.

PHOTO: MAK REMISSA/EPA/CORBIS

MEMORIES CARRIED ON THE WIND

Cambodian survivors of the Khmer Rouge continue to suffer from olfactory-induced panic attacks

During the Communist-inspired revolution that swept Cambodia in the 1970s, more than 1.7 million people died. Among the many slogans driving the Khmer Rouge, the revolution's guerilla force, and its leader, Pol Pot, was one that declared, "What is rotten must be removed."

In their quest to remove *all* people they considered rotten, the Khmer guerillas inflicted a legacy of brutality on those who survived. For some, that continuing cruelty has taken the form of olfactory-induced panic, triggered by such trauma-laden smells as decaying bodies, gas-fueled pyres, and the sulfur and charred vegetation of mortar attacks. Many survivors are so shackled to these olfactory memories that a whiff of the most innocent odor—composting trash, fumes escaping a car's gas tank, a burning cigarette—pulls them into panicked states of vivid recall.

To understand better the mechanisms behind olfactory-induced panic attacks, Devon Hinton, an HMS associate clinical professor of psychiatry at Massachusetts General Hospital, interviewed Cambodian refugees whose attacks had led them to a psychiatric clinic in Lowell, Massachusetts. Hinton, together with collaborator Mark Pollack, an HMS professor of psychiatry at the hospital, uncovered a complex network of causes—a multimodal model that combined symbolic, social, and psychological influences.

To help sufferers gain control of their flashbacks, the researchers recommended a therapeutic schema that included teaching victims to graft troubling odors to pleasant experiences, to develop a coherent narrative for discussing their fears, and to practice mindfulness exercises for relaxation and control.

The scientists also called for more investigations into olfactory-triggered panic attacks and their influence on victims of trauma and post-traumatic stress disorder.

—Ann Marie Menting

EXPERTS IN THE FIELD: For very different reasons, neurobiologist Rachel Wilson and one-year-old Flower are both associated with the olfactory sense.

ON THE SCENT

Scientists are creating artificial noses to diagnose disease

When making diagnoses, doctors have long followed their noses. Hippocrates noted the body odor of his patients when identifying ailments. More than a millennium later, the Persian physician Avicenna used the smell of a person's urine to detect illness. And in the early age of the house call, physicians made sniffing patients part of their routine.

At first whiff, such practices might reek of superstition, but intuitively and scientifically, they make sense. The bodies of sick people produce volatile chemicals that are identifiable by smell. People with diabetic ketoacidosis, for example, often have fruity-scented breath, while those with chronic kidney failure emit a fishy odor.

Hoping to make use of these chemical fingerprints, researchers are exploring ways to sniff out disease. Some are studying the abilities of cancer-sniffing dogs, which have been shown to diagnose illness with surprising success. Others have spurned the hairy and unpredictable business of doggy diagnostics in favor of artificial noses, hoping to develop noninvasive devices for detecting disease. Although some devices are now being tested, their development is stunted by a fundamental lack: Relatively little is known about our sense of smell.

Enter Rachel Wilson, an HMS associate professor of neurobiology and one of a growing number of scientists now focusing on olfaction. Often considered the neglected stepsister of sensory research, olfaction has grown substantially as a field since the first olfactory receptor genes were discovered in 1991. That discovery opened the door for Wilson and others to study our sense of smell at the molecular level.

Wilson's team studies the relatively simple olfactory system of the fruit fly, *Drosophila melanogaster*. The team investigates how the nervous system collects olfactory information, and how that information is processed as it

PHOTO: WEBB CHAPPELL; FLOWER'S APPEARANCE COURTESY OF CURIOUS CREATURES

moves from the primary sense organs to the decision-making centers of the brain.

In insects, the primary sensory organs are olfactory receptors on the antennae (as opposed to receptors in the mammalian nose). Wilson's team puffs odors at the antennae and, with the help of fine electrodes, makes electrical recordings of the neuron activity both in the receptors and in the brain as information is passed along for processing. By labeling specific groups of neurons with green fluorescent protein, and by manipulating or knocking out certain populations of neurons, the team is able to see how those neuron groups respond when fruit flies encounter odors. As the scientists tinker with each distinct group, they can begin to make inferences about the roles those neurons play in the olfactory system.

"We're asking a number of basic questions," Wilson says. "How does a neuron respond to odors? What odors does it respond to? How does it help to encode the olfactory world? And why does it respond that way?"

Answering such questions will help researchers understand how the nervous system identifies scents, but it won't necessarily explain our more complicated responses to odors. With that in mind, Wilson's lab has branched into behavioral experiments. In these studies, they observe how fruit flies respond to odor stimuli. They monitor flies in flight, for instance, to see how flight patterns change as the flies detect smells in the air. The researchers also spy on the flies as they navigate to competing odor sources.

Ultimately, complex behavioral questions such as these may prove most relevant to the development of artificial noses. Learning how the brain identifies smells should be useful not only for designing devices that can diagnose illness, but also for recognizing and tracing odors to their sources, important goals in fields such as environmental quality management and law enforcement.

Wilson believes that the differences between insect and mammalian anatomy can benefit artificial nose research. Her lab has found, for example, that fruit flies respond rapidly to airborne odor filaments. These thread-like plumes emanate from odor sources, much like smoke plumes rising from a candle. Since insects smell with their antennae, they gather information from these odor filaments on contact. As they fly into the plumes, the fruit flies alter their flight path and wing-beating rate, actions that tell researchers that the insects have detected both an odor and its source.

Mammals, in contrast, detect odors through respiration. Not only do we dilute and mix odors when we inhale, but we also disrupt the integrity of odor filaments. (Imagine taking a suction cup to that plume of smoke!) Given that the concentrations of these filaments provide clues about the direction of an odor source and its distance, the mammalian system seems comparatively ill equipped for odor detection and navigation. That's why Wilson is surprised that more developers aren't thinking in terms of the insect system when conceiving of artificial noses.

"Artificial nose developers are designing systems that tend to draw air in through the device's sensors, as if it's respiration," Wilson says. "They should be working in parallel on systems in which sensors respond to filaments quickly, without creating turbulence, because you can learn a lot by observing those filaments."

Wilson predicts medicine's return to the olfactory sense as a diagnostic tool. "It has just seemed too uncouth to be sniffing patients," she says, referring to past practices. "But to avoid using our sense of smell is to throw away valuable information—and real potential applications."

—Veronica Meade-Kelly

Learning how the brain identifies smells should be useful not only for designing devices that can diagnose illness, but also for tracing odors to their sources.

Get a Whiff of This!

- **In *Remembrance of Things Past*, Marcel Proust dwells on the deep, emotional recollections that scents can trigger. Such memories turn out to have a biological basis. Unlike other senses, our sense of smell has a direct line to the emotional center of the brain; the olfactory bulbs protrude into its limbic region.**

- **Some sensations associated with odors are tactile, not olfactory. The burn of hot pepper, the soothing coolness of menthol, and the tear-inducing sting of chopped onion all result from irritation of the trigeminal nerve system, which senses pain and temperature in the nose and face.**

- **Human sperm have odor receptors, suggesting that sperm may locate ova by scent.**

- **Humans have approximately a thousand different odor receptors corresponding to different genes, roughly 35 percent of which are active. In canines, 85 percent of olfactory receptor genes function, accounting for dogs' superior sense of smell.**

- **Although our preferences for aromas are weighted by experience, there's evidence that they are, in part, genetic. Identical twins tend to share the same opinion of the polarizing scent of cilantro, whereas fraternal twins' predilections often differ.**

PHOTO: STEVE NICOLL/ISTOCKPHOTO.COM

(CAN'T GET NO) OLFACTION

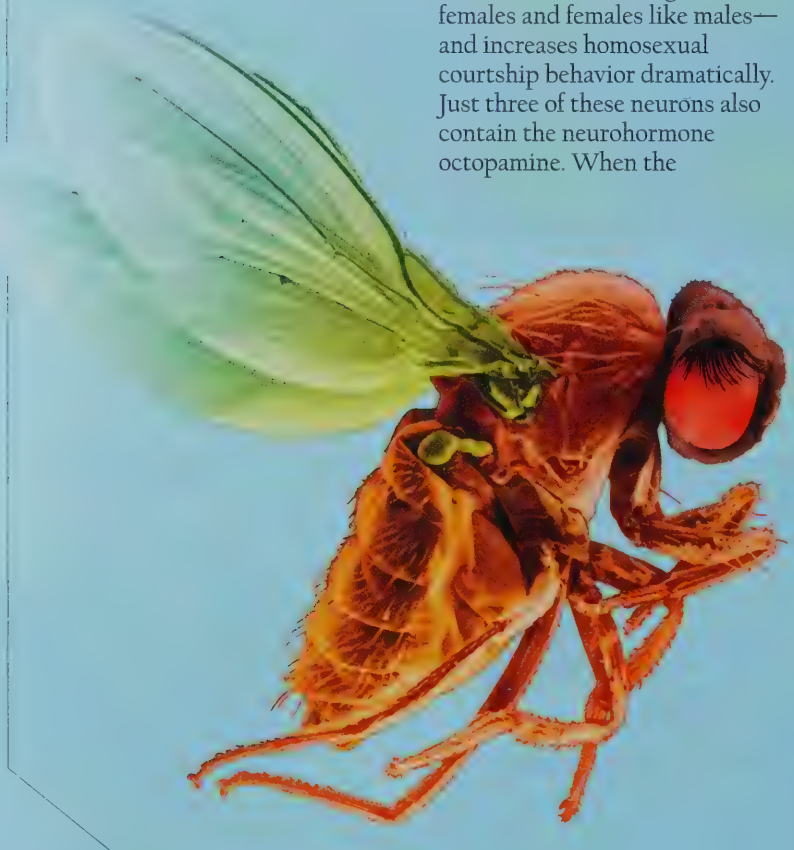
Sure, she's pretty. But how does she smell?

Hey, Miss! You, with the googly red eyes! Wanna dance?

Wouldn't it be nice if you could manipulate another's mood with a waft of your own perfume, turning a stranger from standoffish to sweet? Sirens since Cleopatra have tried, with mixed results. Yet the fly and mouse manage handily. The question is, How?

Ask Edward Kravitz, the George Packer Berry Professor of Neurobiology at HMS, who investigates how innate behaviors such as mating, fighting, foraging, fending off suitors, and evading predators get wired into the brain's neural network. In the fruit fly, *Drosophila melanogaster*, as in humans, the sense of smell plays a key role in regulating behavior. Creatures communicate and influence one another's actions through chemicals called pheromones, which members of a species secrete onto their bodies or into the environment. Neurohormones produced by brain cells, including serotonin and dopamine, also serve important roles in directing behavior.

To study how genes that dictate pheromone production orchestrate complex rituals of courtship and aggression, Kravitz and colleagues tinker with fly DNA using standard techniques—and then watch what happens. Altering a gene called *fruitless*, which is found in about 2,000 neurons in fly brains, makes males fight like females and females like males—and increases homosexual courtship behavior dramatically. Just three of these neurons also contain the neurohormone octopamine. When the researchers either altered *fruitless* or lowered octopamine levels, male flies began courting in the midst of battle.



"We can change the mix of pheromones on females to that of males, to prompt females to fight like males," Kravitz notes. "We can even explore how a male might respond when confronted by a female that smells or behaves like a male."

The Kravitz lab has generated thousands of fly genotypes, each with different mutations. "One by one, we can ask what each neuron does," Kravitz says. Tweaking a few serotonin-producing neurons ratchets up aggression, for example, and manipulating a hundred provokes bizarre, seemingly unrelated behaviors.

Can novel experiences override fly routines engraved in DNA millions of years ago? What happens when an amorous fly receives an unexpected whack upside the head from his ladylove? For those curious about the unfolding fruit-fly drama, answers are expected later this year.

Sharing a fascination for how the brain translates pheromones and other olfactory signals into specific behaviors is Sandeep Robert "Bob" Datta, who joined the HMS neurobiology department last year as an assistant professor. Before beginning his work with *Drosophila*, Datta mastered laser microscopy in the laboratory of HMS Professor of Neurobiology Bernardo Sabatini. Using optical methods he devised himself, he studied neural circuits along which pheromones in flies generate innate sexual behaviors.

Datta has since used his novel laser tool to trace pheromone signals from any of 50 different neuron populations in the fly's nose-equivalent, the antennae, to the fly brain's smell center, the olfactory bulb, then onward and upward into the cerebral cortex, which orchestrates behavior. When odor receptors on a group of neurons detect a potential mate, they propel signals along their axons to the olfactory bulb. The axons converge within a single ball-like structure, the glomerulus, which serves as a way station for sensory information.

Datta found he could trace signals from a single glomerulus into the cortex and link them to a specific behavior. By tinkering with fly genes, he could prompt particular groups of olfactory neurons to turn fluorescent green upon exposure to laser light.

"As one would expect, patterns of branching neurons differ in female and male flies, reflecting sex-specific behaviors," Datta notes. In males, he found, a certain pathway prevented male–male courtship. In females, that pathway proved critical to their receptivity to males' advances.

Scientists with whom Datta has shared his techniques have begun exploring not just smell, but also taste, hearing, and vision in the fly. These days, Datta does his own neural tracing in mice, whose nervous systems more closely mirror those of humans, asking such questions as: Why is a lemon's scent behavior-neutral for mice, while fox odor compels them to scamper? Can we map the neural pathway for fear? Can we modify it genetically?

Such questions could one day illuminate our understanding of phobias and post-traumatic stress disorder, Datta notes. For now, he says, "I want to crawl through the brain—the amygdala, the hypothalamus—to see where the information goes."

—*Karin Kiewra*

PHOTO: © DENNIS KUNKEL MICROSCOPY, INC./VISUALS UNLIMITED/CORBIS

GOODNESS NOSE: Olfactory disorders that limit, alter, or eliminate our ability to partake in airborne luxuries—and receive warnings of danger—reduce our quality of life, underscoring the need to develop therapies for smell loss.

PHOTO: BAMBU PRODUCTIONS/THE IMAGE BANK/GETTY IMAGES

STOP MAKING SCENTS

Quality of life can take a nose dive when illness blocks the olfactory sense

It's a subtle sense, the sense of smell. We tend not to give it much thought, or we think of its role as circumscribed, reserved for savoring the little luxuries of life—the perfume of violets, the aroma of hot chocolate, the milkiness of a newborn. Yet the olfactory sense protects and serves us—allowing us to detect the whiff of leaking gas, for example, or the notes in the concert of flavors on the tongue.

So it's not surprising that patients with olfactory disorders that reduce their ability to smell report a slump in life's quality. Such is the case in the absence of the sense of smell that describes anosmia, the dimming of it that is hyposmia, the altering of it that is parosmia, or the conjuring of it that characterizes phantosmia.

Therapies to correct wayward scents lag, however, a fact that led Eric Holbrook, an HMS assistant professor of otology and laryngology at the Massachusetts Eye and Ear Infirmary, to review what was known about the causes and treatments of smell disorders. In his look at the literature, Holbrook found that the vast majority of olfactory dysfunction cases result from head trauma, upper-respiratory infections, or chronic rhinosinusitis and polyp formation.

Underscoring the importance of isolating cause, Holbrook cites links between neurodegenerative diseases and olfactory dysfunction as well. The literature he reviewed indicates that olfactory biopsies may aid in diagnosing early-stage Alzheimer's disease. And although a range of studies show Parkinson's close association with olfactory loss, Holbrook's analysis of those findings indicates that smell loss can predict development of the disease if the loss manifests within a seven-year window before motor issues arise.

Therapies for olfactory loss from non-neurological causes focus on the surgical removal of blockages and on steroid use, with improvements from oral steroids outstripping those from topical sprays used alone or in combination with oral forms.

With continued research on how smell loss happens, Holbrook notes that better interventions can be developed, returning the delights and the warnings of odors back into more lives.

—Ann Marie Menting

there's no accounting for taste.

Picky eating comes in many flavors. ~ *by* Perri Klass

If you listen to their parents, it's hard to know where all the picky eaters come from. One mother told me that she has happily dined on *natto* in Japan (that would be stinky fermented soybeans), *pastilla* in Morocco (a pigeon pastry laced with sugared cinnamon), and incendiary curries in Sri Lanka.

So how did she produce a son who starts to wail whenever he's urged to eat anything that isn't fried and smothered in ketchup? It wasn't an exam-room encounter, but I asked my usual pediatrician questions—is he healthy, is he growing normally—and I found myself wondering what food tastes like to that child, and then thinking about how taste develops—and I don't just mean taste in the most literal receptors-in-your-tongue sense.

PHOTO: ROSS WHITAKER/THE IMAGE BANK/GETTY IMAGES

each acolyte of the white diet seems to invent it anew, starting with rice cereal, then moving on to other varieties of pap.

Taste also refers, of course, to our opinions and preferences—our *style*. In this, the senses seem to have a hierarchy. You may be able to convince yourself to gaze at Kandinsky when you prefer Rembrandt, you can listen with anthropological curiosity to your adolescent's idea of good music, you can brave quick whiffs of a perfume you would never choose for yourself, and you can stroke a fabric that's rough to the touch. You can't, however, chew your way through something you detest with a genuine smile. Taste, when it's really taste-with-your-tongue, is more profound and visceral than that.

Taste is a frequent topic in pediatric clinics because so many children drive their parents crazy with their finicky eating. There are countless flavors of picky eating, and all seem heartfelt; the children aren't just jerking their parents around. When my journalism students write personal essays, they often recount food aversions from childhood. No one understood, no one believed, but they abhorred chocolate, or fruit, or some other food widely considered delectable. The more limited their palate, the more clearly they remember the injustice of being misunderstood, pressed into trying a despised morsel, forced into the same defensive conversation over and over.

We pediatricians take it as our business to direct parents on how to start their babies on solid foods. We tend to believe that you should begin by offering children fruit purees and work your way slowly toward anything that's sharp or spicy or bitter, anything that's been seasoned or doctored. But not all children have read the playbook. Some snatch barbecued spareribs off a mother's plate before they have any words (that was my daughter), or beg for spoonfuls of a peppery stew, or lick the deli mustard off a father's pastrami sandwich.

Other children reject almost everything, according to their own mysterious neuronal code. Refusing anything new and different is normal for toddlers; hence the standard pediatric advice to keep reintroducing the same delicacy. But as toddlers grow into children, some of them just continue to shake their heads, *no, no, no*. We all know picky-eating archetypes: nothing too hot or too cold, nothing with texture, nothing *green*. One nine-year-old I know will send back a plate of French fries (his favorite and, at times, only reliable food) if the restaurant, in an upscale excess of enthusiasm, has flecked them with fresh parsley.

And then we have the infamous white diet, the ultimate picky-eater state, more extreme even than the anti-green league. These kids eat white bread, noodles, chicken fingers, French fries (if left unblemished), and, of course, vanilla ice cream. Each acolyte of the white diet, though, seems to invent it anew, cutting his teeth, so to speak, on rice cereal, then moving on to other varieties of pap, whether served hot or cold, loose in a bowl or fried in strips. The true white-diet child even avoids ketchup (how loud, how red, how tangy!).

Picky eaters demand custom-crafted meals, force their parents to provide crackers as survival rations at restaurants and birthday parties, and engender a certain moral righteousness in observers. The world is full of people who will assume your picky eater is all your fault. You didn't set limits, did you? You caved and catered, didn't you?

Most children outgrow at least some of their finickiness and learn to savor a little more of what the world has to offer. But there certainly are adults who still carefully avoid many of the foods that others relish, scanning the menu for something plain and broiled, requesting sauce on the side, *because you never can tell*. The sensory input that brings each of us the world doesn't bring us all the same story when it comes to spicy, pungent, sour, or even sweet.

I have watched parents struggle for years with children who refuse even to sample foods that delight the rest of the family. I have worried about the tension that develops between parent and child, and I have tried my best to help parents avoid turning meals into battles. I have marveled at the apparent ability of a child to develop along a normal growth curve, extracting a full range of nutrients from a diet of macaroni and applesauce—and only one brand of applesauce at that. In extreme cases, I have worried about a child's growth and health and hematocrit. It's hard to look at a picky eater and appreciate the rich individualities of taste and preference. And yet, the picky eaters among us, children and adults, do at least assure us that our tongues are our own.

Perri Klass '86 is a professor of journalism and pediatrics at New York University. A contributor to Food & Wine *and a former contributor to* Gourmet, *she is the mother of three adventurous eaters.*

PHOTO: ANN CUTTING/BRAND X PICTURES/GETTY IMAGES

THE PHANTOM GOURMET

Taste comes unbidden to some people with mental disorders

Mmm. That first sip of coffee in the morning. The taste of butter on sourdough toast, perhaps with a dab of raspberry jam. Flavors can make a person's day—or ruin it, if they arise unbidden. For about 7 percent of patients with schizophrenia and other psychotic disorders, gustatory hallucinations—phantom tastes that arrive suddenly and fade just as quickly—are a common and disturbing part of life.

Moreover, most phantom tastes are far from delicious, says Kathryn Lewandowski, an HMS instructor in psychology at McLean Hospital, who studies psychotic patients to assess the type and range of hallucinations they experience. Rather, the tastes tend to be unsavory and confusing.

"Some people with gustatory hallucinations do experience the taste of specific foods," Lewandowski says. "But usually they can't identify the taste; it's just generally unpleasant."

Clinicians have traditionally associated gustatory hallucinations—along with hallucinations of smell and touch—with brain tumors and lesions rather than with psychotic disorders. As a result, such phenomena often escape detection. With her study suggesting that gustatory hallucinations are associated with specific types of delusions and an earlier-than-usual onset of psychosis—a possible harbinger of more severe illness—Lewandowski advises clinicians to ask patients whether they have ever experienced such sensations.

"Patients don't always report them freely," Lewandowski says. "To fail to ask about them misses information that may be clinically relevant, not just for diagnosis but also for identifying possible treatments."

Lewandowski and colleagues plan to continue correlating these unusual sensory experiences with other clinical symptoms and to use neuroimaging data in the hope of pinpointing early signs of mental illness.

—Elizabeth Dougherty

Breath by Chocolate

Your mother told you not to inhale your food, but if you want to indulge in the pleasures of chocolate without the attendant calories, you may just want to take a whiff. David Edwards, a member of the Wyss Institute for Biologically Inspired Engineering at Harvard, has created a mini-inhaler—dubbed Le Whif—that shoots a chocolate mist into the mouth, mimicking, he says, the experience of savoring the real thing.

Edwards, whose science background involves the development of inhalers for drug delivery, conceived of Le Whif when chatting with a chef friend about food and technology. "With medical inhalers, you want the aerosol particles to enter the lungs, not the mouth," he explains. "It was a simple adjustment to design an inhaler so particles are released in the mouth, not the lungs."

The result is a gadget that delivers the high-intensity flavor of chocolate, coffee, and other epicurean delights. Also in the works: Le Whaf, a device that disperses liquid particles into the air, making it possible to "drink" by breathing.

Although critics argue that Le Whif is simply a gimmick, Edwards considers it the product of a union between science and art. "This is just one more way of experiencing food," he says. "It can make some culinary encounters quite different, which is fun."

ILLUSTRATION: LEIGH WELLS; PHOTO: YOON S. BYUN/LANDOV/BOSTON GLOBE

A PINCH OF SALT

The secret to this magical ingredient remains elusive to scientists

Modern chemists know better than to wave a pipette or gloved finger near their mouths. But in 1879, curiosity trumped safety—and produced a sweet surprise.

Johns Hopkins chemists Constantin Fahlberg and Ira Remsen discovered saccharin in an accidental tasting. The reports vary, but only in the details—in one account, Remsen transferred the compound from laboratory equipment to hand to dinner roll to mouth; according to another account, Fahlberg's taste traveled from pencil tip to tongue. The serendipitous discovery led to four patents.

But how, exactly, did these chemists detect that sweet taste physiologically? None of the cellular receptors involved in triggering the brain to detect a sweet sensation on the tongue were known until this century. In fact, none of the cellular receptors for sweet taste were identified until researchers—including a team led by Linda Buck, then an HMS professor—discovered them in 2001.

Today, scientists have identified receptor genes for four of the five tastes: bitter, sweet, sour, and umami, or savoriness. The cells that make up our taste buds express these genes to create receptors that detect the molecular tastants and trigger a signal to the brain.

What remains to be understood is the one flavor used to heighten the taste of everything, from cookies to grilled steak to butter: salt. "Candidate salty receptors have been proposed, but it isn't clear that these are in fact the key mediators of salt taste," says Stephen Liberles, an HMS assistant professor of cell biology who worked with Buck on the taste receptor studies. Liberles's interest in the function of such receptors stems from his ongoing investigation into how sensory cues govern our behavior.

Understanding these various taste receptors—the channels leading to our enjoyment of flavorful foods and our rejection of vile ones—could help researchers develop safer tools than their own tongues for taste-testing new compounds.

—Elizabeth Dougherty

Menu Matters

You study a restaurant menu and decide to order steak rather than salmon. But when the waiter describes the lobster special—which, after all, is seafood, too—suddenly lobster trumps steak. Without reconsidering the salmon, you order lobster, all because of a process called transitivity.

Transitivity underlies rational economic choice. If you prefer lobster to steak and steak to salmon, then you will prefer lobster to salmon.

Work completed in the laboratory of HMS Professor of Neurobiology John Assad suggests that transitivity is encoded at the level of individual neurons in the orbitofrontal cortex. These neurons behave in a menu-invariant way. That is, the neurons respond the same to steak regardless of whether it's offered against salmon or lobster.

"This study provides a key insight into the biology of our frontal lobes and the neural circuits that underlie decision making," Assad says. "We can, in fact, compare apples to oranges, and we do it all the time. This research sheds light on how we make these types of choices."

Scientists have linked faulty decision making evinced by such behaviors as eating disorders and compulsive gambling to frontal lobe damage. And researchers are just beginning to probe normal decision making at the level of individual neurons, venturing into the neuroeconomics field.

—Alyssa Kneller

PHOTOS: MICHAEL ROSENFELD/PHOTOGRAPHER'S CHOICE/GETTY IMAGES; MARCEL PELLETIER/ISTOCKPHOTO.COM

TOUGH TO SWALLOW

Genetics plays a role in picky eating habits

The proof is in the pudding. In the children's book *The Luck of the Loch Ness Monster*, picky eater Katerina-Elizabeth dumps her oatmeal out the porthole of an oceanliner, and a sea worm no larger than a thread gobbles it up. The nourished worm, now as thick as yarn, begins following the ship. Each morning, as Katerina-Elizabeth flings her oatmeal, the worm lengthens and fattens. It follows the ship up a river and into a lake, where Scottish children are lobbing not only dreaded oatmeal but haggis and suet pudding as well. Thus fortified, the worm becomes the legendary Loch Ness Monster.

"Oatmeal is like slug slime, only lumpier," says Alice Flaherty '94, the book's author and an unrepentant picky eater. "My parents would boil Scottish steel-cut oats for nearly an hour, and I would watch in disgust as the concoction belched steam bubbles into the air."

When she was little, Flaherty's father told a version of the sea-worm story to try to coax her into eating oatmeal. "Although I loved the story, it didn't make me love oatmeal," she says. "Now I have twin girls. One's a picky eater like me, the other a normal eater like my husband. That got me interested in the biology of pickiness."

People often blame finicky eating on children's willfulness, says Flaherty, an HMS assistant professor of neurology at Massachusetts General Hospital. "Much pickiness is genetic, though," she says, "and can even help children stay healthy."

Most picky eaters have a "supertaster" gene. If, like one-quarter of the population, you have two copies of the gene, you taste flavors strongly, especially bitter compounds in foods such as broccoli. If you have neither copy, you can't detect bitter flavors. The medium tasters—half the population—can taste the bitterness but don't mind it.

"The supertaster gene may be a leftover from our evolutionary past, preventing us from eating toxins and spoiled food," Flaherty says. "I only wish I'd known to argue that as a kid, when I faced all those globs of oatmeal."

Taste the Burn

There's a certain magic in Thai food. The fire hits hard, then fades. The taste buds beg for more. This enchanting cycle of fleeting and repeating self-torture and sweet relief continues, until—the bowl of Tom Yum soup nearly drained, the last grains of rice all but devoured—you take your final peppery, lemongrassy bite.

The ancients who crafted these exotic herbal concoctions were culinary alchemists, pairing their seasonings to agonize—and to entice. Little did they know that, centuries later, scientists would be working to tease apart the secrets of their spicy mastery.

Chemicals called tastants cause the burning sensation and subsequent cooling relief so common in Asian cooking. Capsaicin, a chemical in peppers, triggers sensations of heat and pain by stimulating taste receptors on the tongue. Citral, a chemical in lemongrass, squelches that heat.

As fans of hot, spicy food may know, a sip of water amplifies the peppery burn by welding the capsaicin to the taste receptors. Milk dampens the burn as its fatty lipids flush away the compound.

"Citral makes it not so hot, but in a different way," says Stephanie Stotz, a research fellow in cardiology at Children's Hospital Boston. Stotz has found that citral blocks G protein-coupled receptors—transient receptor potential ion channels in taste buds—only after they have been activated and depolarized by, say, a tastant such as capsaicin. Stotz has shown that citral obstructs these open taste detectors in model cells.

But the way citral works has a temporal component: It allows a quick surge of taste response—the burn—then soothes it for an extended time—the cooling relief.

The molecular mechanisms governing the cooling effect of citral-like compounds remain a mystery. Yet unraveling these mechanisms could help lead to new pain medicines, says Stotz. "We're eating these compounds for a reason," she adds. "They're helping us dampen pain and heighten pleasure."

—Elizabeth Dougherty


EDGAR POE
ADVENTURES
GORDON PYM

What can phantom sensations teach us about how our brains talk to our bodies?

The Man in the MIRROR

by ATUL GAWANDE

He was 48 when he made passing mention of an odd pain to his internist. For at least 20 years, H. said, a mild tingling had run along his left arm and down the left side of his body, and, if he tilted his neck forward at a particular angle, it became a pronounced, electrical jolt. The internist recognized this as Lhermitte's sign, a classic symptom that can indicate multiple sclerosis, vitamin B12 deficiency, or spinal-cord compression from a tumor or a herniated disk. An MRI revealed a pea-sized mass of dilated blood vessels pressing into the spinal cord in the patient's neck. A week later, the tumor ruptured.

He was raking leaves when suddenly he felt an explosion of pain, H. told me when I visited him at home two years ago. Once the swelling subsided, a neurosurgeon removed the tumor. The operation was successful, but afterward H. began experiencing a constellation of strange sensations. His left hand felt cartoonishly large—at least twice its actual size. He developed a constant burning pain along an inch-wide ribbon extending from the left

Researchers have begun to believe that perception is the brain's best guess about what is happening.

side of his neck down his arm. And creeping up and down along the same band was an itch that no amount of scratching would relieve.

For eleven years, the slightest pressure could trigger an excruciating flare-up—a cool breeze across the skin, the brush of a shirtsleeve. "Sometimes I feel that my skin has been flayed and my flesh is exposed," H. said. "Sometimes I feel that there's an ice pick or a wasp sting. Sometimes I feel that I've been splattered with hot cooking oil."

For all that, the itch was harder to endure. H. developed calluses from the incessant scratching. He tried all sorts of treatments—medications, acupuncture, herbal remedies, lidocaine injections, electrical-stimulation therapy. But nothing worked, and the condition forced him to retire in 2001.

A new understanding of perception has emerged in the past few decades, and it has overturned centuries-long beliefs about how our brains work. We believed that the hardness of a rock, the coldness of an ice cube, the itchiness of a sweater were picked up by our nerve endings, transmitted through the spinal cord, and decoded by the brain.

Our assumption had been that the sensory data we received from our eyes, ears, nose, fingers, and so on contained all the information that we needed for perception, and that perception worked something like a radio. Yet, as scientists set about analyzing sensory signals, they found them to be radically impoverished. The information we work from is poor—a distorted, two-dimensional transmission with entire spots missing. So the mind fills in most of the picture.

The fallacy of reducing perception to reception is especially clear when it comes to phantom limbs. Doctors have often explained such sensations as a matter of inflamed or frayed nerve endings in the stump sending aberrant signals to the brain. But surgeons' efforts to cut back on the nerve typically produce relief only briefly.

Moreover, the feelings people experience in their phantom limbs are far too varied and rich to be explained by the random firings of a bruised nerve. People report not just pain but also sensations of sweatiness, heat, texture, and movement in a missing limb. Children have used phantom fingers to count and solve arithmetic problems.

More recently, researchers have begun to believe that perception is the brain's best guess about what is happening in the outside world. The mind integrates scattered, weak, rudimentary signals from sensory channels, information from past experiences, and hard-wired processes, and produces a perceptual experience full of brain-provided color, sound, texture, and meaning.

The theory has begun to make sense of some bewildering phenomena. Among them is an experiment that Vilayanur Ramachandran, director of the Center for Brain and Cognition at the University of California, San Diego, performed with volunteers who had phantom pain in an amputated arm. The volunteers each put the surviving arm through a hole in the side of a box with a mirror inside, so that, peering through the open top, they could see the real arm and its mirror image. Ramachandran then asked them to move both the intact arm and, in their minds, the phantom arm. The patients regained the sense that they had two arms. Even though they knew it was an illusion, the exercise provided immediate relief.

This experiment suggests that when your arm is amputated, nerve transmissions are shut off, and the brain's best guess often seems to be that the arm is still there, but paralyzed, or clenched, or beginning to cramp. The mirror box provides the brain with new visual input—however illusory—suggesting motion in the absent arm. The brain incorporates the new information into its sensory map; it guesses again, and the pain dissipates.

The morning I visited H., he told me that he thought his problem was basically a "bad switch" in his neck where the tumor had been, a kind of loose wire sending false signals to his brain. But I told him about the increasing evidence that our sensory experiences are not sent to the brain but originate in it. When I mentioned that he might want to try the mirror-box treatment, he agreed.

He brought a cheval glass down to the living room, and I had him stand with his chest against the side of it, so that his troublesome left arm was behind it and his normal right arm was in front. He tipped his head so that when he looked into the mirror the image of his right arm seemed to occupy the same position as his left arm. Then I asked him to wave his arms as if conducting an orchestra.

At first, he expressed disappointment. "It isn't quite like looking at my left hand," he said. But then suddenly it was.

"Wow!" he said. "Now, this is odd."

After a moment or two, I noticed that he had stopped moving his left arm. Yet he reported that he felt as if it were still moving. What's more, the sensations in it had changed dramatically. For the first time in eleven years, he felt his left hand "snap" back to normal size. The burning pain diminished. And the itch was dulled.

"This is positively bizarre," he said.

He still felt the pain and the itch in his neck and shoulder, where the image in the mirror cut off. And, when he came away from the mirror, the aberrant sensations in his left arm returned. He began using the mirror a few times a day, for fifteen minutes at a stretch. After a couple of weeks, his hand returned to feeling normal all day long.

The mirror also provided him with the first effective treatment for his flare-ups. Where once he could do nothing but wait for the torment to subside, he now just pulls out the mirror. "I've never had anything like this before," he said. "It's my magic mirror."

Atul Gawande '94, MPH, is a surgeon at Brigham and Women's Hospital, an associate professor of surgery at Harvard Medical School, an associate professor in health policy and management at the Harvard School of Public Health, and a staff writer for The New Yorker. *His latest book,* The Checklist Manifesto: How to Get Things Right *(Metropolitan Books, 2009), explores strategies for preventing medical errors. This essay was excerpted and adapted with permission from "The Itch" in the June 30, 2008, issue of* The New Yorker.

PHOTOILLUSTRATION: SOUTHERN GOTHIC, 2001 © MAGGIE TAYLOR

THE PAIN OF OUR EXISTENCE

The instinct to respond to potential danger helps keep us alive

How the body feels sensations—a brush of fingertips or the heat from a nearby iron—is a complicated business. *Why* it feels, however, is simple: Our survival depends on it.

Not only do we need to know what might harm us, we must also remember how to respond to dangers. Fortunately, biology has provided us with the perfect protection mechanism. It is called pain.

"Pain is such a fundamental sensation," says Anne Louise Oaklander, an HMS associate professor of neurology and director of the Nerve Injury Unit at Massachusetts General Hospital, "that rare individuals born without pain sensation often die in childhood."

"Pain signals also are tied into learning and memory," she adds. "We might forget the name of our fourth-grade teacher, but nobody forgets that a flame burns."

Thus acute pain, the short, perhaps excruciating, reaction to an environmental cue, helps keep us alive and away from harm. Pain becomes a problem, however, when its useful unpleasantness becomes unending.

Acute pain might cause us to yelp, recoil, or exhibit other help-eliciting behaviors, but in chronic pain, these behaviors extinguish. Yet the pain itself—unrelenting tensed muscles or burning sensations, for example—remains distressingly insistent although unapparent to others.

Unraveling the neurologic basis for chronic pain drives the investigations of many neuroscientists, including Oaklander. Her research has yielded insights into its causes and cleared some paths toward its better diagnosis and treatment.

One area in which Oaklander and others have provided clarity is our understanding of the characteristics and operations of pain-registering nerve cells in the skin called nociceptors. When damaged by direct inflammation or other insult, these sensitive sentinels can misfire, bombarding the brain with unfocused messages. Nociceptor degeneration from injury or illness also can miscue the spinal cord and brain to signal pain after such nonpainful stimulation as light touch—or even without any sensory stimulation. This inappropriate signaling by central pain neurons deprived of normal input from periphery neurons, what Oaklander calls "phantom-skin pain," is akin to the excessive firing of the brain's pain neurons when the body loses limbs or other parts.

Proper diagnosis is critical to stemming this cascade of effects. Yet nociceptors are the merest of threads: They do not even register in standard nerve-damage tests such as reflex checks of the knees or electromyography and nerve conduction studies. So Oaklander uses a skin-biopsy technique that uses immunolabeling to highlight the endings of viable nociceptors, allowing researchers to determine their densities. Low densities indicate nerve damage as the cause of chronic pain.

Oaklander expects future studies to lead to new diagnostic tools, identification of new pain diseases, and better understanding of nociceptors and their role in chronic pain.

"Neuropathic pain is still in the mid-twentieth century," says Oaklander. "It's the Wild West of medicine."

—*Ann Marie Menting*

FOCAL POINTS

Touch awareness may help rewire the brain

If movement and a light touch can help us learn to train our brains to control body sensations, can they also enable chronic pain sufferers to learn to alleviate their own misery? To explore this theory, Catherine Kerr, an instructor in medicine at Beth Israel Deaconess Medical Center, turned to tai chi, a Chinese slow-motion meditative exercise that fosters body awareness by teaching its practitioners to focus on the movements and sensations of their bodies. In neurological terms, such concentration places an attentional spotlight on the body and contributes to complex motor learning.

Kerr engaged a small group of seasoned tai chi practitioners in a movement regimen that encouraged them to focus attention on their extremities, particularly their fingertips. After several weeks, Kerr measured the tactile acuity of members of the group and matched controls. She found that the tai chi practitioners, particularly the older ones, had improved their ability to detect the subtle variations of a roughened surface with their fingertips, suggesting that body-awareness activities may enhance sensory acuity.

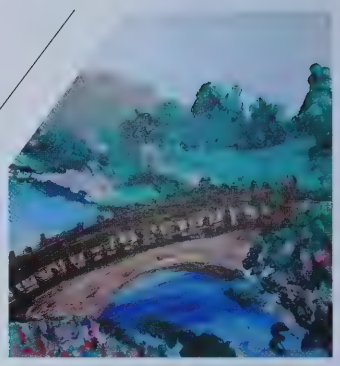
In related research, Kerr and colleagues at HMS and MIT assessed the literature on such touch-healing therapies as Reiki, therapeutic touch, and mindfulness meditation. They found signature elements of these practices to also be important to neural mechanisms of sensory reorganization.

The researchers speculated, for example, that the repeated tactile stimulation administered during touch healing helped guide attention away from existing pain, reduce stress, and deemphasize the expectation of pain. Together, these outcomes may allow the brain to rewire "maladaptive" cortical connections formed in response to unremitting pain. In addition, touch healing may be a preventive: Its practitioners can be taught how to avoid establishing neural connections that result in unending pain.

"Touch has been neglected as a source of health and healing," says Kerr. "I believe these studies begin to show how we might work with touch, not only to better understand touch healing, but also to help relieve suffering by addressing the cognitive aspect of pain."

—Ann Marie Menting

FORM AND FUNCTION: Movement exercises such as tai chi may help modify chronic pain pathways in the brain.



Magic Touch

During his first five years of life, light and dark helped him navigate his world. Then, his blindness became complete. Yet even as his sight quenched, Esref Armagan drew, using touch to capture the external world, then re-creating those mental images in sand, his fingers tracing the edges to make sure the pictures matched those in his brain.

Today, Armagan renders his mental representations onto paper fixed to a rubberized tablet. His fingers are guided by his pencil's depressions, allowing him to produce an image resembling the one his brain has built.

To investigate how this artist's brain constructs a visual world from touch alone, Alvaro Pascual-Leone, an HMS professor of neurology at Beth Israel Deaconess Medical Center, and colleagues turned to functional magnetic resonance imaging. As expected, as Armagan drew, the frontal–parietal region of his cortex became active—this area is known to transform perception into two-dimensional imagery and to coordinate sensory–motor information in sighted and nonsighted artists alike. What surprised the researchers was the robust activity in Armagan's occipital cortex, a region devoted to visual processing.

These findings suggest to Pascual-Leone that the occipital cortex plays a key role in supporting mental representations—even without the aid of vision.

—Ann Marie Menting

PHOTO: KEREN SU/CORBIS; PAINTING: ESREF ARMAGAN; DIGITAL IMAGE: © ZAFER KIZILKAYA/IMAGES & STORIES

PHOTO: AMIT GUPTA/REUTERS/CORBIS

DIGITAL CONNECTIONS

Touch can reshape the brain's connections, helping it interpret what might be lost to other senses

Ask Alvaro Pascual-Leone what touch is and you will get a clear—and captivating—definition.

"We're tempted to think that touch is like the other senses," says Pascual-Leone, an HMS professor of neurology at Beth Israel Deaconess Medical Center, "simply a specialization of our nervous system that allows us to capture such aspects of reality as pain, pressure, and temperature. But as we have found, this doesn't allow us to fully appreciate the role of touch in brain development. When we see, hear, smell, and taste, our mind's fingers touch our mind's eyes, ears, nose, and tongue, shaping the way we interpret those sensations."

Pascual-Leone refers here to work his team has done to assess the plasticity of the human visual cortex. For their study, the researchers initially monitored visual-cortex activity in normally sighted participants as they performed a tactile exercise. Then for five days and nights, some participants wore light-blocking blindfolds. During this period, all participants underwent intensive tactile training that included Braille instruction.

After five days, the researchers found that, when compared with the sighted group, the blindfolded participants showed a greater ability to discriminate among Braille characters, a behavioral improvement linked to activity in their visual cortices. This ability diminished within one day, leading the researchers to marvel at the capacity of the visual cortex to reallocate its resources rapidly to accommodate nonvisual information—and then return to original functioning.

"Maybe the visual cortex is visual because we have vision," says Pascual-Leone. "It may be functionally capable of processing any other type of information. And perhaps this plasticity is true of every part of the brain."

Pascual-Leone's research on the excitability of the visual cortex underscores this concept. His team measured the minimum level at which the visual cortices of participants could perceive a flash of light delivered alone and when coupled with a glancing touch to the hand.

Then the researchers administered both stimuli at levels below human perception—and found that the participants could still accurately report the light flashes. Without the below-threshold touch, however, the lights remained unseen. The visual cortex had changed, says Pascual-Leone, increasing its ability to interpret the light stimuli by combining two imperceptible sensations—one visual and one touch-based.

—Ann Marie Menting

Pressure Points

When a woman who had experienced a blockage of the blood supply to the right portion of her thalamus came to the attention of a group of researchers, they were intrigued. The thalamus is recognized as a key relay for sensory information en route to the cerebral cortex, yet few opportunities exist for exploring this midbrain structure's role. What, the researchers wondered, might a stroke to one of its two lobes reveal about thalamic function?

To investigate this question, the international team of researchers engaged the woman in a six-year study. The team monitored her behavioral responses to light, tones, and mild electrical stimuli as well as her sensory responses to such stimuli using a connectional imaging technique developed by team member Van Wedeen, an HMS associate professor of radiology at Massachusetts General Hospital. Midway through the study, something extraordinary surfaced: The woman reported that she could feel sound.

Unlike, say, visual–visual synesthetes, who see letters of the alphabet as particular colors, people with sound–touch synthesia are exceedingly rare. Yet the woman was adamant: An array of sounds, including the voice of a radio announcer, elicited a skin tingling on her left side, the one affected by the blockage.

The woman's brain showed that the neural pathways between the damaged portion of her thalamus and her cortex had become disorganized and diffused, while pathways between the companion lobe and the cortex remained robust. Such restructuring suggests that sensory pathways to the cortex may dynamically remodel after being damaged, reflecting the brain's remarkable ability to compensate for injury.

—Ann Marie Menting

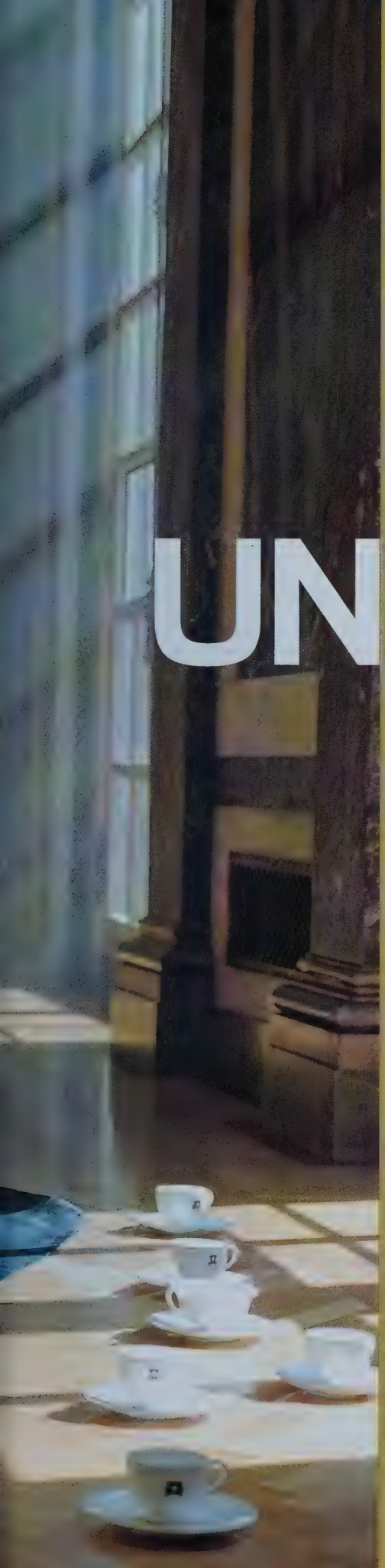


PHOTO: ZOE WITH TEAPOT ON HEAD, BURDEN MANSION, NEW YORK CITY, 2006. © RODNEY SMITH

Synesthesia helps the brain luxuriate in metaphor

by ALICE FLAHERTY

UNCOMMON SENSE

Sir Francis Galton, the Victorian anthropologist, performed arithmetic by smell. In an experiment to prove he could banish all visual and auditory associations with numbers, he taught himself to add and subtract small sums by imagining aromas. Two whiffs of peppermint, for example, equaled one whiff of camphor, while three whiffs of peppermint amounted to one hit of carbolic acid. Encouraged by the results, he began tasting sums, with salt, sugar, and quinine in place of integers.

Some people experience a more natural—and neurally based—commingling of the senses through synesthesia, a phenomenon in which one modality, such as vision, produces an automatic, involuntary perception in another, such as hearing. An estimated 1 percent of people have some form of synesthesia, which runs in families and appears more often in women.

My own form is the most common: grapheme-color, in which letters of the alphabet evoke specific hues. For me, the

Most people seem to have mild synesthesia, perceiving high-pitched sounds as bright and low-pitched sounds as dark.

letter *f* is pine green, while *a* is a dark manila. For years I assumed that such mental images stemmed from my play with letter-shaped refrigerator magnets as a child. Only after I learned about synesthesia in a college lecture did I dig up my old magnet set and realize that the colors didn't match the ones lodged in my brain.

Synesthesia comes in many forms. Spatial-sequence synesthetes experience three-dimensional perceptions; the 1950s, for instance, may appear near the ground. Numbers and letters gain personalities in ordinal-linguistic personification synesthesia. And in lexical-gustatory synesthesia, words cause taste sensations. One synesthete reports that she loves to chant the word *because*; to her, it tastes like a Mars bar.

Out of Your Senses

Most people seem to have mild synesthesia, perceiving, for example, high-pitched sounds as bright and low-pitched sounds as dark. Similarly, we all tend to hear certain speech sounds as sharp and others as rounded. In a 1947 study, the Gestalt psychologist Wolfgang Köhler showed people jagged and smooth shapes, then asked which were called *takete* and which *maluma*. Participants consistently—and across languages—paired the jagged image with the otherwise meaningless sound *takete* and the smooth image with *maluma*.

Nearly a century earlier, poet and philosopher Benjamin Blood had described how certain words conjure the objects they describe. The sound *tub* suggests "short and stubby," he declared, while *icicle* conjures up "spindling and slim."

Blood then went on to offer an exuberant description of generalized synesthesia. "Consider," he said, "the use of the words *entrails, reins, bowels*—all good in scientific and social discourse, but for some unmentionable reason classic culture draws the line at *guts*!" When asked what the trouble with *guts* was, Blood replied that it was vulgarized by the absurd genius of the guttural *u*, which he described as "a huge, lubberly, blundering dunderhead, a blubbering numskull and a dunce, ugly, sullen, dull, clumsy, rugged, gullible, glum, dumpish, lugubrious…a musty, fussy, crusty, disgusting brute…."

Apart from such broad associations as sound with luminosity and syllables with shape, synesthetic perceptions are idiosyncratic: One grapheme-color synesthete's *m* is mauve while another's is chartreuse. Yet links remain remarkably consistent. A true synesthete will retain the same color–sound associations across decades.

Key to Your Art

Synesthesia is an example of what psychiatrists call hyper-associativeness, often seen in creative people. Vivid synesthesia, in fact, is disportionately likely among artists. The painter Wassily Kandinsky, poets Arthur Rimbaud and Charles Baudelaire, and composers Leonard Bernstein, Nikolai Rimsky-Korsakov, and Franz Liszt were all synesthetes. For the novelist Vladimir Nabokov, a long *a* had "the tint of weathered wood" while a hard *g* evoked "vulcanized rubber" and *l* was "noodle-limp."

People without synesthesia sometimes envy those with it. But hyperassociative thinking can also appear in psychosis, and synesthetes are more susceptible to mental illness.

Not surprisingly, synesthetes have better memories in the modalities for which they are synesthetic, presumably because those sensations are multimodal and vivid. But their memories may become full of irrelevant flashes of color and sound, as jangled as Times Square at night. In one poignant case study, the Russian neuropsychologist Alexander Romanovich Luria described the mind of "a little man with a perfect memory" whose mnemonic powers stemmed from multimodal synesthesia. Nothing was forgotten; everything was connected. The man, who had started life as a writer, became overwhelmed by the tangle in his head and finished his life doing memory tricks in a circus.

Living in Metaphor

At first glance, synesthesia may seem merely vivid metaphor, elaborate figures of speech rather than direct experiences or brain states. But a closer look suggests the opposite: Many metaphors are directly synesthetic, such as "her voice was sharp" and "his name leaves a bad taste in my mouth."

Synesthesia appears to have a clear neurological basis, as, in fact, does metaphor. When synesthetes with colored hearing undergo functional magnetic resonance imaging while listening to letters being spoken, they show more diffuse patterns of brain activity than nonsynesthetes. Like nonsynesthetes, their primary auditory cortex is active while their primary visual cortex is not. Yet synesthetes also have activity in several higher-level visual areas in the temporal and parietal cortices—despite the absence of visual stimuli.

Additional functional imaging studies show that synesthetes have greater white matter connectivity, the anatomical basis of their hyperassociativeness. Other research suggests that synesthesia may be the result of overwiring in the brain, in which some neurons that should connect to just one sensory center instead connect to two or more. This increased connectivity can foster delusions, such as when a racehorse's name smells like money. But the overbranched neurons may also foster creative thinking by integrating apparently unrelated sensory inputs, memories, ideas, and actions.

No doubt much about synesthesia remains to be discovered. In the meantime, its very existence stimulates one of our most enduring senses: our sense of wonder.

Alice Flaherty '94, PhD, is an HMS assistant professor of neurology at Massachusetts General Hospital.

FLIGHT OF FANCY: Dragonflies can see in ultraviolet light.

EXTRA SENSORY PERCEPTIONS

Aristotle missed the mark when he named only five

Ask Harvard Medical School researchers how many senses humans have and you're bound to receive a range of answers. This lack of consensus isn't limited to Harvard: Neurologists and others who study perception have long disagreed on the number of senses we possess to help us navigate our way through life.

No one doubts the Big Five. Vision, hearing, smell, taste, and touch have been classified since the days of Aristotle, who reportedly catalogued them himself. From the yeasty aroma of freshly baked bread, to the silky feel of a cat's sleek coat, to the Technicolor brilliance of a sunset, most of us continually experience our world through the major senses.

These days, however, some scientists believe that this quintet can be split into subgroups. Sight, for instance, may be divided into perceptions of brightness, color, and depth. Other researchers argue that true senses are bodily systems consisting of a group of sensory cell types that not only respond to a specific physical phenomenon but also correspond to a particular region in the brain. Using that definition, many neurologists recognize additional human senses.

Equilibrioception. Whether you're slaloming down a slope or strutting down a street, this sense—otherwise known as balance—helps keeps you upright. Although vision plays a role in equilibrioception, the vestibular system of the inner ear is mainly responsible.

Nociception. If you've touched a boiling kettle or stubbed a toe, you're likely all too familiar with nociception, the sense of pain. Recent research shows that what was once viewed as a subjective experience related to touch is, in fact, a distinct phenomenon that corresponds to a specific area in the brain.

Proprioception. Close your eyes and touch your fingertip to your nose. Quick: Where's your hand? Unless you suffer from a deficit of this kinesthetic sense, you know where your hand is, even though you can't see it. This sense, the awareness of where your body parts are, sounds silly—until you consider that without it, you'd have to constantly watch your feet to make sure they were planted on the ground.

Thermoception. You notice a chill in the air, so you don a jacket on your way to work. Later, as you enter your warm office, you shed that garment. That's thermoception, the sense of heat and cold, which relies on temperature sensors in your skin to keep you from overheating or freezing.

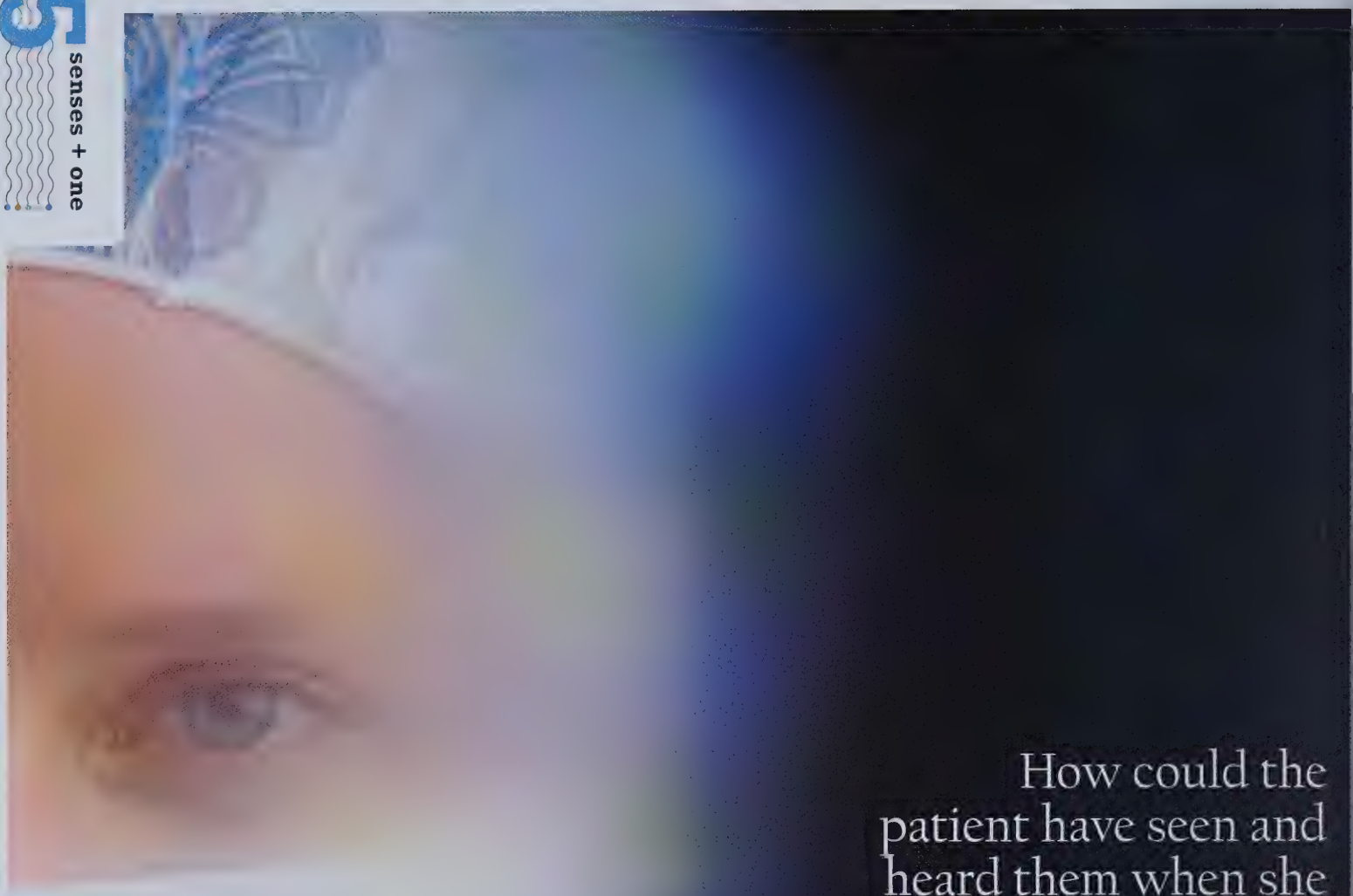
Temporal perception. There's no doubt that the perception of time can be subjective: Three hours spent at a party with friends may speed by, while a three-hour meeting can seem to drag. Yet our sense of time is rooted in biology. Research shows that the basal ganglia and other parts of the brain are responsible.

Interoception. When we take our internal perception into account, we have even more senses. These are linked to sensory receptors found in internal organs, such as those in the lungs that control respiratory rate.

Perhaps most fascinating, though, are the senses we *don't* have. Ever wish you could sniff out hidden objects, see in the dark, or detect magnetic and electric fields? In humans, these senses are the domain of superheroes. Yet they're a natural advantage to some animals. Dogs have an extraordinarily keen sense of smell. Bloodhounds, for example, have noses up to 100 million times more sensitive than ours. Cats can see in just one-sixth the light level we require, while vampire bats and some snakes can see in infrared, and bees and dragonflies can see in ultraviolet. Birds and bees navigate—and migrate—based on their perception of magnetic fields. And sharks can sense changes in electric fields, as can platypuses. Even some plants get in on the act: Venus flytraps can sense vibration, light, water, and odors.

These and other abilities remain a fantasy for humans. Belts and other devices are in the works that may allow us to sense magnetic fields, for example, but their success is still limited. For now, we'll have to continue to rely on our five standard-issue senses. Or is it ten? Or sixteen?

—Jessica Cerretani



How could the patient have seen and heard them when she was clinically dead?

by ALLAN J. HAMILTON

the Sixth sense

By any clinical measure Sarah was dead. Her body had cooled, her heart had stopped, her brain waves had disappeared. During her seventeen minutes as a corpse, a surgical team worked quickly yet carefully to seal off her brain aneurysm.

In a planned cardiac arrest, a cardiopulmonary bypass machine replaces the heart's vital pumping function. Surgery for Sarah's basilar aneurysm required blood flow to stop completely, however, so her surgeons cooled her brain to allow it to tolerate this cessation.

During Sarah's suspended animation, a microphone picked up several murmured conversations. In one, the surgeon asked the perfusionist whether the bypass machine was ready to be restarted; the perfusionist replied that he needed to "blow" it first—to fire it up to ensure any bubbles in the system would clear. In another exchange, a nurse recounted her marriage proposal the night before: the posh restaurant, the one-and-a-half-carat diamond ring, the swain on bended knee, the waiter who tripped over him and fell into the wine case.

When the pump cleared, the perfusionist said, "Thar she blows, captain." The bypass machine churned, and Sarah's blood began flowing again. Her body was gently warmed, and her heart resumed beating. Within minutes, a normal, healthy brain-wave pattern reappeared on the EEG. The operation had proceeded flawlessly.

After several hours in the intensive care unit, Sarah's head cleared. When she sat up to greet her surgeon, she asked whether her aneurysm had blown. He reassured her that the surgery had been "textbook perfect."

"Well, I thought I remembered hearing something 'blow,'" Sarah said. "I thought someone said, 'Thar she blows.' Like in *Moby Dick*."

Her surgeon paled. After explaining his conversation with the perfusionist, he asked whether she had remembered anything else. Not realizing the sheer impossibility of what she had just said, Sarah went on to describe the nurse's proposal, recounting the anecdote nearly word for word, right down to the restaurant's name, the diamond's carat weight, and the waiter's stumble and fall.

It was utterly impossible, from a biochemical, metabolic, or physiologic point of view, for Sarah to have created any memories during her moments of suspended animation. Her brain had been devoid of any discernible electrical activity. Yet she had stored and recalled not only accurate auditory memories, but visual ones as well. She was able to describe the perfusionist's beard, the blonde tendril escaping from the cap of the newly betrothed nurse, and the bypass machine's location in the operating suite—even though the unit had been wheeled in after she had been under general anesthesia for more than two hours.

I was one of many doctors and researchers who soon flocked to Scottsdale, Arizona, to interview Sarah. We pored over the records, listened to the audio track, and watched the video footage of the surgery. Sarah was the equivalent of a valuable archeological find, and we wanted to leave the site fully explored, yet undisturbed. Not only were OR personnel interviewed independent of one another, but they were not allowed contact with Sarah, who was interviewed and videotaped separately.

We began our inquiry with a vague, almost smug, scientific curiosity, confident we'd find an explanation for this mystery. But as rational explanations faded one by one, we began to wonder whether we had encountered something unique, wondrous even. Could we be looking at the neurophysiologic equivalent of the Holy Grail?

According to one theory, Sarah's brain—and the conscious mind it produced—had traveled beyond its physical and physiological confines. A group of physics researchers posited another notion, as radical as the first: that the OR conversations had survived as discrete quanta of energy, available for later plucking as memories.

No matter how we sought to explain it, Sarah's experience seemed to suggest that the mind, the essential repository of consciousness, could separate from the very brain that created it and live without neuronal support, like a light bulb illuminated without any source of power.

What, I wondered, should those of us in the medical field do with such unsettling disturbances, such seeming ripples of the supernatural? Ignore them? Or should we declare them simply to be a puzzling mixture of science and spirit? Can we not allow ourselves to entertain the possibility that the supernatural, the divine, and the magical may all underlie our physical world? Can we not admit that we yearn to glimpse the mystery of the spirit?

I'm reminded of a carved angel perched near the top of the spire of the Notre Dame Cathedral in Paris. Turned away from the cross just above her, she is shielding her eyes with her arm, as if fearful of being struck blind while witnessing the glory of God. Perhaps Sarah's experience offers a glimpse into the mysteries of our minds, but one that upends our world of scientific convention and constraints.

Like the cautious angel, we must content ourselves with oblique glimpses and trust that as much as we can withstand has been revealed. We cannot grasp the mystery. Or measure it. Or map it. But maybe that has to suffice for now.

Allan J. Hamilton '82 is a professor of neurosurgery and a clinical professor in the radiation oncology, psychology, and computer and electrical engineering departments at the Arizona Health Sciences Center in Tucson. *This essay was excerpted and adapted from* The Scalpel and the Soul: Encounters with Surgery, the Supernatural, and the Healing Power of Hope, *by arrangement with Jeremy P. Tarcher, a member of Penguin Group (USA) Inc.,*

PHOTO: RYAN MCVAY/PHOTODISC/GETTY IMAGES

ASSEMBLY INSTRUCTIONS
HOW TO BUILD A BETTER DOCTOR

FIRST, THE DISCLAIMER. Harvard Medical School—like medical schools around the world—has been building great doctors for decades, even centuries. But as biomedical research discoveries continue to mushroom, today's doctors must be nimbler than ever.

In response to this growing pressure, several years ago the School reengineered its curriculum for the first time in nearly a generation. The latest reform—the New Integrated Curriculum—builds on the foundation of the previous one, the New Pathway, by better integrating lessons taught in the classroom with those learned in the clinic. The ultimate aim: superbly trained, clinically and socially responsible physicians with a deep understanding of the underlying science of medicine.

The first HMS class to have progressed through the entire new curriculum will graduate this spring. To commemorate this milestone, we offer instructions for assembling doctors who are well prepared for the challenges of today's medicine.

FIRST CLASS: Ishani Ganguli, pictured right, began her medical career with the HMS Class of 2010, whose members gave continuous feedback to the architects of the New Integrated Curriculum during its first two years.

1 Before beginning assembly, select the highest-grade material available.

The importance of choosing excellent medical school candidates cannot be overstated. HMS admissions committees follow a simple formula of seeking aptitude and attitude, idealism and intellectual curiosity, scholarly promise and compassionate engagement.

2 Gather the right tools.

Proper physician assembly requires proper instruction, technologies, and community. Through the Academy, HMS works to build better teachers by identifying best practices, fostering innovation, and rewarding excellence in teaching. In addition, today's students can avail themselves of a range of educational aids, from state-of-the-art simulated patients to iPod-downloadable, multimedia-enhanced lectures. And the School encourages its students to join in creating new knowledge rather than just mastering it, by offering opportunities to participate in world-class research.

3 Ensure proper alignment of individual parts.

Teach your doctor not only the fundamentals of medicine but the big picture as well through a cohesive curriculum. At HMS, the first two years of training now build from molecules to cells to organisms, with seamless transitions to anatomy, pathophysiology, and clinical care. Afternoon tutorials on drug-resistant tuberculosis, for example, now follow morning presentations on lung physiology.

PHOTO: KATHERINE LAMBERT

4 Maximize the operating system (and not just for surgeons).

"The essential quality of the clinician is an interest in humanity," Francis Peabody, Class of 1907, famously declared, "for the secret of the care of the patient is in caring for the patient." The School now integrates the science of medicine with the sociology of medicine. All HMS students study medical ethics, global health, social medicine, and health care policy.

5 Follow quality assurance guidelines.

Integrate the content students learn in the clinic. The Principal Clinical Experience, the School's new longitudinal, multidisciplinary clerkship, now places students in a single hospital for an entire year. This experience not only affords them rich mentoring opportunities, but also allows them to work with the same patients over time, replacing snapshots of understanding with streaming video. Compared with their peers in traditional clerkships, students in the new clerkships report more confidence in their clinical skills, an improved ability to integrate science with clinical medicine, and a better understanding of how the socioeconomic context affects patients.

6 Avoid placing a one-size-fits-all label on your completed doctor.

Recognize that there's no one ideal path to becoming a physician. Some hope to become leaders, research investigators, or academics; others want to safeguard the health of individuals, communities, or the entire world. Celebrate their diversity and nurture their talents, for the secret of the care of the doctor is in caring for the doctor.

SMART SCIENCE

THE FUTURE OF MEDICINE IS NOW

Smart Clothing

With the hope of one day filling closets with assistive medical devices woven into textiles, affixed to leggings, or stitched into shoes or gloves, Harvard Medical School researchers are designing apparel that weaves technology with fashion to enhance patients' lives.

A. Helping Hands

Improving the functioning of a patient's hands and upper limbs following stroke or other neurological insult is the goal of research in the laboratory of Paolo Bonato, an HMS assistant professor of physical medicine and rehabilitation and director of the Motion Analysis Laboratory at Spaulding Rehabilitation Hospital. Although patients can improve arm and hand movement by performing tasks that involve reaching for, grasping, and retrieving objects, it can be difficult to ensure that patients practice those tasks correctly and repeatedly. So Bonato and his team developed a sensorized glove that, when combined with a robotics platform, guides a patient in exercises designed to rebuild function. A proven aid to adults with traumatic brain injury, the glove may, Bonato hopes, also help those for whom stroke and neurological problems have impaired or limited upper-limb function.

B. Good Vibrations

Is it easier to stay upright if the ground beneath your feet moves a wee bit? It may be for older people and for those whose peripheral-nerve sensitivity is dulled by diabetic neuropathy or stroke, says synthetic biologist James Collins, a member of the faculty at the Wyss Institute for Biologically Inspired Engineering at Harvard. Collins, who explores how mild vibrations can stimulate the peripheral nervous system, tested whether vibrating insoles placed in shoes and under the soles of the feet could help elderly people with these disorders maintain their balance while standing still. Sole-based vibrations did the trick, tweaking the performance of nerves enough to decrease postural sway even among healthy participants serving as controls.

C. Little Leggings

The vision of a second skin, one that embraces the legs and directs a damaged nervous system to learn to function better, powers the research of Eugene Goldfield, an HMS assistant professor of psychology at Children's Hospital Boston and an associate faculty member of the Wyss Institute. As Goldfield sees it, this skin will serve as a new type of orthotic to aid brain-injured infants, including those with cerebral palsy. Conceived of as a soft, light fabric studded with tiny, programmable sensors that can sense a limb's attempts at movement, Goldfield's smart leggings will take motion information and feed it to the sensors, which in turn will boost the effort of the child's muscles. By allowing muscles to experience proper mechanics, the leggings aim to help rewire the developing brain of the very young—and improve locomotion.

ILLUSTRATION: ZARA PICKEN

D. Tell-Tale Threads

Threading clothing with sensors that can track the well-being of people with stroke, chronic obstructive pulmonary disease, and Parkinson's disease is central to the research efforts of Paolo Bonato, who directs motion analysis research at Spaulding Rehabilitation Hospital. "In designing wearable technologies, we always start with the specific challenges of the clinical problem, such as when to make needed changes to medications or therapies," says Bonato. In one study, people with Parkinson's disease performed tasks while wearing sensor-studded clothing that recorded movement patterns; data analyses provided clues to the severity of various symptoms. "Wearable technology can provide objective measures on a continuous basis," says Bonato. "This information gives physicians a detailed picture of whether a medication is effective or in need of adjustment."

E. Dancing Shoes

A shoe that may one day help the elderly and those with Parkinson's disease remain upright and on the straight and narrow was developed as part of a pilot study by a research team from Massachusetts General Hospital and the Massachusetts Institute of Technology. For its study, the team outfitted footgear with such orientation aids as gyroscopes and accelerometers. Dubbed the GaitShoe, the footgear linked on-board orientation instruments to insole-embedded pressure sensors. The sensors then transmitted vital postural data to remote computers through wireless telemetry. Tests of a prototype of the GaitShoe, says Donna Moxley Scarborough, a physical therapist at the hospital and a member of the research team, showed that wearers could roam well beyond the confines of a testing laboratory yet remain monitored. In the future, the team hopes to refine the shoe-sensor system to include musical prompts. Such cues could help Parkinson's patients and perhaps others achieve walking tempos that would, through biofeedback, help them become more sure-footed.

—Ann Marie Menting

Five Questions for Michael Greenberg

Name: Michael Greenberg

Title: Chair of the Department of Neurobiology, Harvard Medical School

Quote: I expect progress in neuroscience to accelerate in this century, just as cancer biology and molecular biology did in the second half of the last.

THE COMING REVOLUTION

This has been called the century of the brain. How accurate will that label prove to be?

Very. We're poised for a revolution of discovery. Many neurological and psychiatric diseases still need to be understood, and many treatments and cures need to be developed. With proper investment, we'll see astounding discoveries unfold, enabled by microscopy, imaging, and genomic technology. I expect progress in neuroscience to accelerate in this century, just as cancer biology and molecular biology did in the second half of the last.

What role do you expect Harvard Medical School to play in that revolution?

A key to the neurobiology department's future lies in its past: One of the most profound neuroscientific discoveries of the twentieth century was made here, when David Hubel and Torsten Wiesel showed, in the visual system, that our interaction with our environment helps shape the development and function of the nervous system.

This department will continue to work at the frontier of discovery. Our broad research goal is to understand the development and function of the brain at the level of basic science, but with an eye toward finding therapies and cures for neurological and psychiatric disorders, such as Alzheimer's, Parkinson's, and schizophrenia.

What are the most common misconceptions about the brain?

One assumption has been that you're born with a finite number of neurons, and as you age those neurons die. We now know that to be false; we grow new neurons throughout life.

Another mistaken belief has been that neurological disorders result primarily from neuronal cell death. We're learning, though, that this might not be true for many diseases. We suspect that in some cases neuronal loss is the result of a loss or malfunction of synapses.

A third misconception, one that's just now changing, is that developmental disorders of the nervous system—such as Rett syndrome and Fragile X syndrome—are so devastating that no treatment could ever help. We believed that once the brain failed to develop normally, we couldn't do anything. But evidence now suggests—especially in disorders resulting from a disruption of experience-dependent aspects of brain development—that the brain is waiting for a signal. It's almost as though the brain is frozen in time.

If we can figure out how to trigger that signal, devise an alternative route, or bypass it, we can make progress. I was recently talking with a friend whose brother-in-law has been incapacitated by Fragile X syndrome for decades. I was able to tell her about a drug being tested in mice that might eventually help him.

What are the greatest challenges?

One key challenge is understanding how neural circuits work—not just the synapse, but also the rules for circuit formation and function. We also need to expand our understanding of how experience shapes our brain by delving into the mechanisms of gene activation and expression.

What would readers be most surprised to learn about you?

I guess it would be that I didn't train as a neurobiologist. My doctoral and postdoctoral work was in cancer biology. But I sometimes view my nontraditional path to neurobiology as an advantage. Unencumbered by the assumptions of classical training, I can bring a fresh perspective to the field. As a result, not many researchers are taking the approach my lab is taking to understanding the brain.

Also surprising, I suppose, is that I come from a family of artists and teachers. I didn't grow up with a fascination with science; I wasn't the kid pulling apart bugs. But when I first learned how DNA works, I became hooked, and science became my passion.

PHOTO: JOSHUA TOUSTER

Erik Alexander, MD, Assistant Professor of Medicine, teaches students Andy Schissler and Xin Gao, both HMS Class of 2011, during their hospital rotations.

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